Case-Based Gynecological Oncology

Kavita Singh
Bindiya Gupta
Editors

Springer

Case-Based Gynecological Oncology

Kavita Singh • Bindiya Gupta
Editors

Case-Based Gynecological Oncology

Springer

Editors
Kavita Singh
Birmingham City Hospital
Birmingham, UK

Bindiya Gupta
UCMS and GTB Hospital
New Delhi, India

ISBN 978-3-031-36178-4 ISBN 978-3-031-36179-1 (eBook)
https://doi.org/10.1007/978-3-031-36179-1

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Case-based gynaecological oncology follows our first book *Gynecological Oncology: Basic Principles and Clinical Practice* ISBN 978-3-030-94109-3, which aimed to develop an easier, more practical understanding of evidence-based management in daily clinical practice. This book helps in practical implementation of the principles and practices of gynaecological oncology, which we had learnt from the first book. This book is a ready reckoner for practising clinicians, easy-to-understand, concise and answers all questions relating to diagnostic investigations and management of a variety of clinical scenarios.

It focusses on clinical management of real-time anonymised clinical case scenarios supported with radiological and intraoperative images. The book is divided into sections based on various gynaecological cancers namely ovarian, endometrial, cervical, vulval and vaginal. A special section has been devoted to rare cancers like sarcomas. Each section covers clinical situations of various histologic subtypes, early and advanced stages, recurrent and metastatic disease.

As the mean age of conception is increasing, we come across many women with genital cancers who wish to preserve fertility and women with cancer during pregnancy. The book details the management and outcomes in different clinical situations in these contexts. Additionally, various techniques of fertility preservation are discussed which are very useful for an oncologist to understand while dealing with cancers in the adolescent and young adult population. As we are in an era of precision medicine, availability of advanced sequencing techniques and immunohistochemistry has given a new outlook to hereditary cancers especially of the ovaries and endometrium. A separate section on hereditary cancers covers counselling.

It is indeed a humbling and emotional moment for both of us to see both the volumes in print, something which we had envisioned three years back. We are extremely thankful to the eminent authors who have kindly contributed to the book, sharing their vast clinical experience and expertise.

Our book is dedicated to our patients who are our constant source of inspiration and learning.

Birmingham, UK — Kavita Singh
New Delhi, India — Bindiya Gupta

Contents

Part I

Case Based Studies: Ovarian Cancer

Management of Adnexal Masses

1

Namita Batra and Bindiya Gupta

Introduction

Adnexal mass refers to the solid/cystic mass of the adnexa i.e. ovary/fallopian tube/surrounding connective tissue and are one of the most common gynecological problems across all age groups, posing both a diagnostic and a management dilemma. Adnexal masses are evaluated to determine the chances of them being benign/malignant or the need for any prompt emergency management (e.g. Ectopic pregnancy/adnexal torsion). The most common type of adnexal masses are ovarian masses with 8–35% incidence in pre-menopausal and 3–17% incidence in post-menopausal women [1]. In this chapter we shall discuss the evaluation of adnexal masses, to estimate the probability of malignancy and their management. The classification of adnexal masses is shown in Table 1.1.

N. Batra · B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_1

Table 1.1 Classification of adnexal masses

Gynaecologic tract masses	Premenopausal	Ovulatory: Functional/corpus-luteal cysts Theca-lutein cysts Polycystic ovaries Pregnancy-related Corpus-luteum of pregnancy Luteoma Decidualization of endometrioma Ectopic pregnancy Hormone stimulated Endometrioma Leiomyoma Infectious/inflammatory Tubo-ovarian mass Hydrosalpinx Benign neoplasms Serous or mucinous cystadenoma Mature cystic teratoma Paraovarian/paratubal cysts Tubal/broad ligament neoplasms Malignant neoplasms
	Postmenopausal	Neoplastic Epithelial neoplasms Germ-cell tumours Sex-cord stromal tumours Non-neoplastic Simple ovarian cysts
Non-gynaecologic masses	Metastatic diseases Abdominopelvic abscess Urinary tract masses Others	
Adnexal mass complications	Haemorrhagic ovarian cyst Ruptured ovarian cyst Adnexal torsion	

Case 1

Age, parity, PS	52 years, P2 + 0, previous one LSCS, ECOG = 1, BMI 29
Presenting complaints	Pain abdomen, abdominal distension, constipation, referred i/v/o abdominal mass History of breast cancer in mother and maternal aunt Examination 10 cm mass in right adnexa solid cystic restricted mobility with nodules in pouch of Douglas. Rectal mucosa free
Co morbidities	None
Transvaginal sonography	Large mass 13 × 12 cm, solid areas present with papillary projections + colour doppler flow increased
CT scan thorax, abdomen, pelvis	Large solid cystic lesion 14 cm, likely arising from right ovary with papillary projections. Peritoneal deposits close to the uterus largest measuring 3 cm with fat planes lost posteriorly with the rectum. Small amount of free fluid in abdomen. Haziness and fat stranding in omentum. Uterus normal. Upper abdomen normal. No lymphadenopathy
Other investigations	CA125: 653 U/ml, CEA: 2.3 ng/ml, CA19.9: 24 U/ml
Surgery	Primary debulking surgery- Total abdominal hysterectomy with bilateral salpingo-oophorectomy+ omentectomy + removal of peritoneal nodules
Histology	High grade serous carcinoma stage 2B, p53 aberrant

Table 1.2 Risk factors for ovarian cancer

	Relative risk	Lifetime probability (%)
Risk factors		
General population	1.0	1.3
BRCA1 mutation		35–46
BRCA2 mutation		13–23
Lynch syndrome		3–14
RAD51C		5.2
RAD51D		12
Infertility	2.67	
Endometriosis	2.04–3.05	
Cigarette smoking	2.1	
Protective factors		
Past use of oral contraceptives	0.73	
Tubal ligation	0.69	
Previous pregnancy	0.71	
Past breast feeding (>12 months)	0.72	
Intrauterine device	0.68	

Q: What Are the Risk Factors for Ovarian Cancer?

The lifetime probability of a women to have ovarian cancer is 1.3%. Predisposing risk factors for ovarian cancers are previous breast cancer in self or a family history of breast /ovarian cancer. The risk factors and protective factors are shown in Table 1.2 [2–9]. A knowledge of these helps in identifying the high-risk population.

Q: What Are the Clinical Features Suggestive of a Malignant Ovarian Mass?

Epithelial ovarian cancer in early stages usually presents with non-specific and vague gastrointestinal, abdominal, and urinary symptoms. The *Goff symptom index suggests that occurrence of any of the eight symptoms including pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full more than 12 times a month for less than 1 year may be considered positive for ovarian cancer* [10].

In advanced cases the presentation is usually with abdominal mass, pain abdomen and ascites. Hormone producing tumours will present with signs of virilisation, heavy menstrual bleeding and post menopausal bleeding.

Findings suggestive of malignancy include presence of ascites, abdominal lump, organomegaly, adnexal masses (unilateral or bilateral, more than 10 cm, fixed or restricted mobility) and nodules in Pouch of Douglas. Other important findings to be assessed are cachexia, presence and severity of pallor, lymphadenopathy (supraclavicular, axillary and inguinal) pedal edema, thyroid swelling and breast lump or nipple discharge [11].

Q: What Are the Differentiating Features of Benign and Malignant Ovarian Masses on Ultrasound?

Transvaginal ultrasonography is the standard first line investigation for evaluation of adnexal masses and pathologies. The main signs suggestive of malignant mass is adnexal mass more than 10 cm with solid cystic areas, with increased colour doppler flow, multiseptate mass with increased septal thickness, papillary projections and presence of ascites [12–15].

In order to ensure uniformity in reporting world over and guide management, International ovarian study group analysis study group (IOTA) simple rules and Ovarian-Adnexal reporting and data system committee (O-RADS US) are used to classify adnexal masses. IOTA group defined a standardized procedure for pre-operative classification of adnexal masses by 10 simple ultrasound rules for predicting benign or malignant ovarian tumors based on ultrasonographic features (Table 1.3) [16–20]. If one or more M features are present in absence of B features it is a malignant mass or if one or more B features are present in absence of M features it is a benign

mass. The sensitivity and specificity of IOTA Simple rules being 93% and 83% respectively [21]. The ORADS systems (Table 1.4) ensures unambiguous sonographic evaluations of ovarian or adnexal lesions assigns them to a risk category of malignancy which then guides the management. The colour score (CS) indicator is classified as CS1: no flow, CS2: minimal flow, CS3: moderate flow, CS4: strong flow. ORADS has a higher sensitivity for malignancy of around 97–98% as compared to the IOTA rules [22].

Age, parity, PS	45 years, parous, ECOG = 2, BMI-29
Presenting complaints	Abnormal uterine bleeding
Co morbidities	Hypothyroidism, fever with splenomegaly, thrombocytopenia, anemia, B/L polycystic kidney
Transvaginal sonography	Uterus bulky, endometrial thickness 18 mm, right adnexal mass of 6X6 cm with solid cystic components (Fig. 1.1)
Endometrial biopsy	Hyperplasia without atypia
CECT abdomen	Right ovarian mass, ascites
Other investigations	CA125: 75.3 U/ml CEA: 2.5 ng/ml CA19.9:228.3 U/ml Inhibin B: 877.9 pg/ml
Surgery	Staging laparotomy: Total abdominal hysterectomy+ bilateral salpingo oophorectomy+ infracolic omentectomy
Histology	Granulosa cell tumour stage IA (Fig. 1.1)

Table 1.3 IOTA B and M rules in imaging for adnexal masses

Rules for predicting malignant tumours (M-rules)	Rules for predicting benign tumours (B-rules)
M1 irregular solid tumour	B1 Unilocular cyst
M2 Presence of ascites	B2 presence of solid components where the largest solid component is <7mm in largest diameter
M3 At least four papillary structures	B3 presence of acoustic shadows
M4 irregular multilocular solid tumour with largest diameter >100 mm	B4 smooth multilocular tumour with largest diameter <100 mm
M5 very strong blood flow	B5 no blood flow

Table 1.4 Scoring systems for risk stratification (ORADS-US)

ORADS score	Risk category IOTA model	Description
0	Incomplete evaluation (N/A)	N/A
1	Normal ovary (N/A)	• Follicle defined as simple cyst ≤3 cm • Corpus luteum ≤3 cm
2	Almost certainly benign (<1% risk of malignancy)	• Simple cyst: – 3–5 cm – >5 but <10 cm • Classic benign lesions: hemorrhagic cyst, dermoid cyst , endometrioma, paraovarian cyst, peritoneal inclusion cyst, hydrosalpinx < 10 cm Non-simple unilocular cysts, smooth inner margin: – <3 cm – 3–10 cm
3	Low risk malignancy (1 to <10%)	• Unilocular cyst ≥10 cm (simple or non-simple) • Typical dermoid cysts, endometriomas, haemorrhagic cysts ≥10 cm • Unilocular cysts of any size with irregular inner wall <3 mm thickness • Multilocular cyst <10 cm, smooth inner wall, colour score 1–3 • Solid smooth, any size, colour score = 1

(continued)

Table 1.4 (continued)

ORADS score	Risk category IOTA model	Description
4	Intermediate risk (10 to <50%)	• Multilocular cyst, no solid component: – ≥10 cm, smooth inner wall, colour score = 1–3 – Any size, smooth inner wall, CS = 4 – Any size irregular inner wall and/or irregular septation, any colour score • Unilocular cyst with solid component, any size, 1 to 3, papillary projections, CS = any • Multilocular cyst with solid component, any size, CS = 1to 2 • Solid, smooth lesion, any size, CS = 2 to 3
5	High risk (> = 50%)	• Unilocular cyst, any size, >4 papillary projections, CS = any • Multilocular cyst with solid component, any size, CS 3 to 4 • Solid smooth, any size, CS = 4 • Solid irregular any size, CS = any • Ascites or/and peritoneal nodules

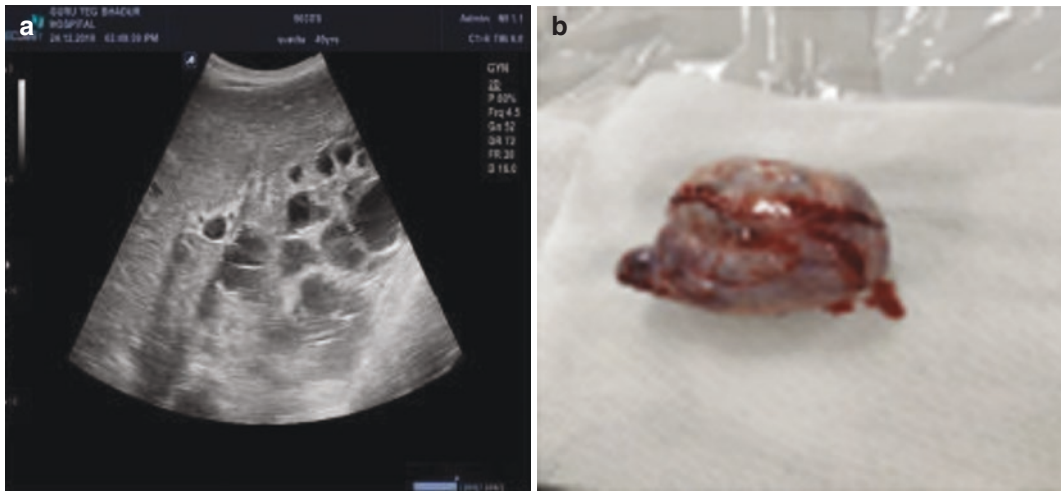


Fig. 1.1 (**a**) Gray scale ultrasound image shows multiloculated solid and cystic mass. (**b**) Gross image shows specimen- encapsulated with smooth lobulated surface, solid and cystic

Case 2

Q: What Are the Hormone Producing Tumors of Ovary? Why Was Endometrial Sampling Necessary in the Present Case?

Ovarian sex-cord stromal tumors are the hormone producing tumors of the ovary. Anti-mullerian hormone (AMH) and Inhibin is produced by granulosa cell tumors, serum estradiol (E2) elevations are seen with granulosa cell tumors and thecomas, testosterone may be produced by sertoli-leydig or Sertoli cell tumours, steroid cell tumours. Estrogen producing tumours present with precocious puberty in pediatric age group and post- menopausal bleeding or heavy menstrual bleeding in post- menopausal and pre-menopausal women respectively. Testosterone producing tumours present with signs of hirsutism and virilization. Other examples of hormone producing tumours are beta–HCG produced by ovarian choriocarcinoma and struma ovarii producing thyroxine.

Endometrial sampling should be performed in premenopausal women with an adnexal mass and abnormal uterine bleeding and in post menopausal women with postmenopausal bleeding associated with thickened endometrium (ET>/=4 mm) on trans vaginal ultrasound to rule out endometrial hyperplasia or endometrial cancer. Endometrial hyperplasia/endometrial intraepithelial neoplasia may be found in 25–50% patients of granulosa cell tumors and endometrial carcinoma in 5–10% of them [23–25].

Q: Discuss the Role of Tumor Markers in Management of Adnexal Masses? Explain the Decision to Decide Which Tumor Marker Is To Be Done?

CA125 is the most commonly used serum marker for ovarian epithelial cancers and plays an important role as an adjunct to imaging in diagnosis of epithelial ovarian cancers (EOC). It is a part of the Risk of Malignancy index (RMI) algorithm (Table 1.5) which is a triage tool for evaluation of adnexal masses. Other markers used for evaluation of EOC are Carcinoembryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) which are especially useful in mucinous tumours to distinguish primary and metastatic tumours. FDA approved HE4 for monitoring of recurrent or progressive disease in patients with EOC, especially in patients with non-elevated CA 125. It is also used as a component of ROMA and serum Overa tests. Risk of malignancy algorithm (ROMA) uses CA125 and HE 4 and depends on menopausal status. The cut offs for premenopausal patient and post menopausal patents are ≥13% and ≥27.7% respectively [26–29].

Beta-hCG, alpha-fetoprotein, Lactate dehydrogenase (LDH) are markers for ovarian germ cell tumours. Alpha fetoprotein is elevated in endodermal sinus tumours while elevated beta-HCG is present in choriocarcinoma of the uterus, embryonal carcinomas, polyembryomas, mixed cell tumours. LDH and placental alkaline phosphatase are elevated in dysgerminomas. It is mandatory to do the germ cell tumor markers in all women with adenexal mass below the age of 40 years.

Inhibin and Testosterone are markers for hormone producing tumours granulosa cell tumor and sertoli leydig cell tumor respectively.

This case serum inhibin was done as the women presented with an adnexal mass with abnormal uterine bleeding and endometrial hyperplasia.

Table 1.5 Scoring systems for risk stratification (ADNEX and RMI) [10–14]

	Predictor variables
ADNEX without CA-125	• Age (years) • Maximum diameter of lesion (mm) • Maximum diameter of largest solid component (mm) • Number of papillary projections • Presence of ascites • Multilocularity (more than 10 cyst locules) • Type of centre (oncology vs others)
ADNEX with CA 125	CA 125 (IU/L) and all the above variables
RMI (risk of malignancy index)	• CA 125 • Menopausal status • Ultrasound score based on five variables: multilocularity, solid areas, bilateral lesion, ascites, presence of metastasis on abdominal USG • RMI=UX CA125X M • U=USG score, no feature = 0 – 1 feature = 1 – >1 feature = 3 • M = 1 for premenopausal, 3 for postmenopausal • RMI < 25 = low risk – 25–250 = mod risk – >250 = high risk for malignancy

Case 3

Age, parity, PS	40 years, parous, ECOG = 1
Presenting complaints	Pain abdomen, BMI 25
Co morbidities	No co-morbidities
Transvaginal sonography	Uterus normal, endometrial thickness normal, left adnexal 14 cm multi septate mass with solid cystic components
Other investigations	Contrast CT scan findings – were concurrent with US findings revealing a complex 14 cm ovarian mas with solid and cystic areas, with normal upper abdomen and bowel, no retroperitoneal lymphadenopathy Upper and lower gastrointestinal endoscopy: normal CA125: 910 U/ml CEA: 29.5 ng/ml CA 19.9: 12000 U/ml CA125/CEA: 30
Surgery	Staging laparotomy - total abdominal hysterectomy, bilateral salpingo oophorectomy+ supracolic omentectomy
Histology	Mucinous carcinoma moderately differentiated stage IIIC

Q: What Additional Investigations Should Be Done When There Is a Probability of Mucinous Ovarian Tumours?

In premenopausal women CA125 lacks specificity/sensitivity for diagnosing ovarian cancer. However, raised CEA in presence of an adnexal mass is highly suggestive of a metastatic/krukenberg or primary mucinous ovarian cancer. Contrast enhanced CT scan of chest, abdomen and pelvis is essential to evaluate upper abdomen and exclude any lesion in the breast, liver, bowel, gall bladder and pancreas which can metastasize to the ovary. Alternatively, PET scan can be ordered to rule out another primary, however it is not cost effective and may have false positive results in case of inflammation or infectious etiology [30].

In addition ratio of CA125 and CEA >25 maybe suggestive of primary ovarian malignancy and <25 is suggestive of GI malignancy [31].

Raised CA19-9 may be increased in secondary tumours from pancreas, gastrointestinal tract and appendix. CA15-3 is elevated in primary breast cancer.

Q: Describe the Triage Pathway of Adnexal Masses Which Will Benefit from Management by a Gynae-Oncologist?

It is well accepted that ovarian cancer outcomes are best when managed by a gynaecological oncologist. To facilitate referral of suspected ovarian cancers to a gynaecological oncologist, there are several risk scoring models which help in triaging these referral pathway for adenexal masses. Women presenting with adnexal masses and in addition have ascites, evidence of abdominal and distant metastasis on cross-sectional imaging, associated with markedly raised CA125 may benefit from referral to a gynaeoncologist care.

Risk of Malignancy index (RMI) algorithm (Table 1.5) is a triage tool for evaluation of adnexal masses. Using an RMI cut-off of 200, a sensitivity of 70% and specificity of 90% can be achieved. Management of cases with RMI of more than 200 will benefit from discussion in a multidisciplinary tumour board meeting and surgery performed by a gynaecological oncologist. Other tools used in triaging are IOTA ADNEX model and ORADS-US (Tables 1.4 and 1.5) [32–35].

ADNEX model not only predicts the risk of benign, borderline or malignant nature but can also predicts the stage of the tumor in cases of suspected malignant masses (stage I/II/ stage III/IV) and also whether the tumor is primary or metastatic. ADNEX model has a sensitivity of 97% and specificity of 71% [36]. The ultrasound images, ADNEX model and the gross specimen is shown in Fig. 1.2.

All adnexal masses with an intermediate risk (10–50%) or high risk (≥50%) of malignancy i.e. ORADS 4/5 should be referred to specialized gynaecological oncologist [37].

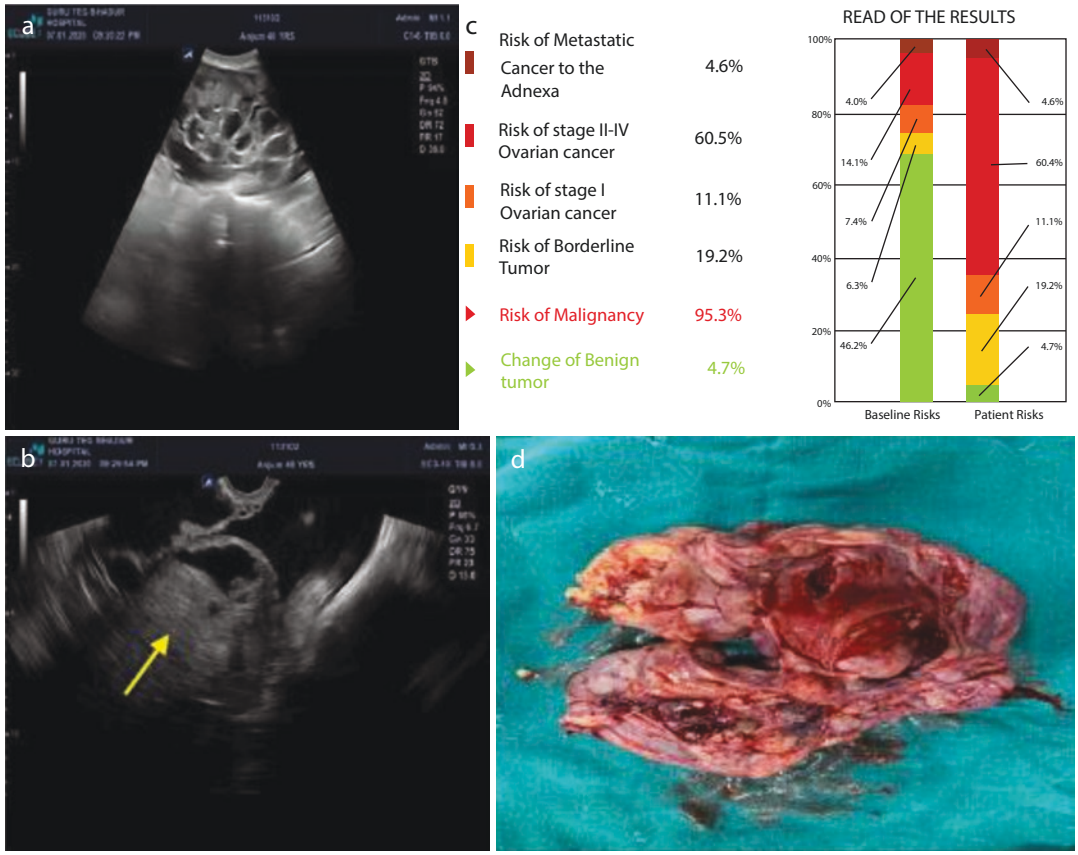


Fig. 1.2 (**a**) Gray scale ultrasound image showing multilocular, numerous thick walled cyst containing fluid of various echogenicities. (**b**) Arrow shows a solid component with papillary projection in the ovarian multicystic mass. (**c**) ADNEX model- risk of malignancy is 95.3%; stage II-IV invasive (60.5%). (**d**) Cut section showing multiloculated cyst with solid areas and mucinous fluid. **Final histopathology- Mucinous cystadenocarcinoma stage IIIc**

Case 4

Age, parity, PS	29 years, P2L0, ECOG = 1
Presenting complaints	Pain abdomen, abdominal mass
Co morbidities	No co-morbidities
Transvaginal sonography	Uterus normal, endometrial thickness normal, large 15 × 10 cm heteroechoic solid cystic mass with multiple septations, B/L ovaries could not be visualised separately
CECT abdomen and pelvis	Large mass occupying the abdomen suggestive of mucinous tumor, no ascites, liver, spleen, gall bladder, pancreas, bowel normal
Other investigations	CA 125: 26 U/ml CEA: 2.3 ng/ml
Surgery	Staging laparotomy with left salpingo-oophorectomy
Histology	Begin mucinous cystadenoma

Q: How Can You Differentiate a Benign and Malignant Mucinous Tumor Based on Clinical Presentation and Ultrasound Findings?

Mucinous tumours represent a spectrum of tumours with benign, borderline and invasive histologic variants. Benign mucinous cystadenomas are large tumors mostly presenting in the 2nd -4th decade. Mean size at presentation is 18 cm, but they can be extremely large filling

the entire abdomino pelvic cavity. Majority are unilateral and are primary ovarian tumours. Figure 1.3 shows the ultrasound, ADNEX score and intraoperative findings of the case to understand the correlation of imaging, tumor markers and gross findings.

Malignant tumours can be unilateral or bilateral and unlike the benign counterparts the mean size of the tumor is around 10 cm. They may be associated with ascites and constitutional symptoms. Malignant mucinous ovarian carcinoma can be metastatic especially if they are bilateral.

Radiologically, as discussed above the IOTA M and B rules are good parameters to differentiate the benign and malignant masses if done by an expert sonographer.

Q: Role of Cystectomy Versus Oophorectomy? What Is the Impact of Rupture During Removal?

In mucinous cystadenomas, cystectomy can be performed for relatively smaller masses when there is a possibility of having a normal ovarian tissue. If cystectomy is performed and it is incompletely removed with remnants of cyst wall remaining then it will mostly recur and also with transformation to BOT/malignancy therefore complete removal is essential.

Cyst rupture for benign lesions does not cause intraperitoneal seedling but in malignant tumours, cyst rupture upstages the disease from 1A to 1C.

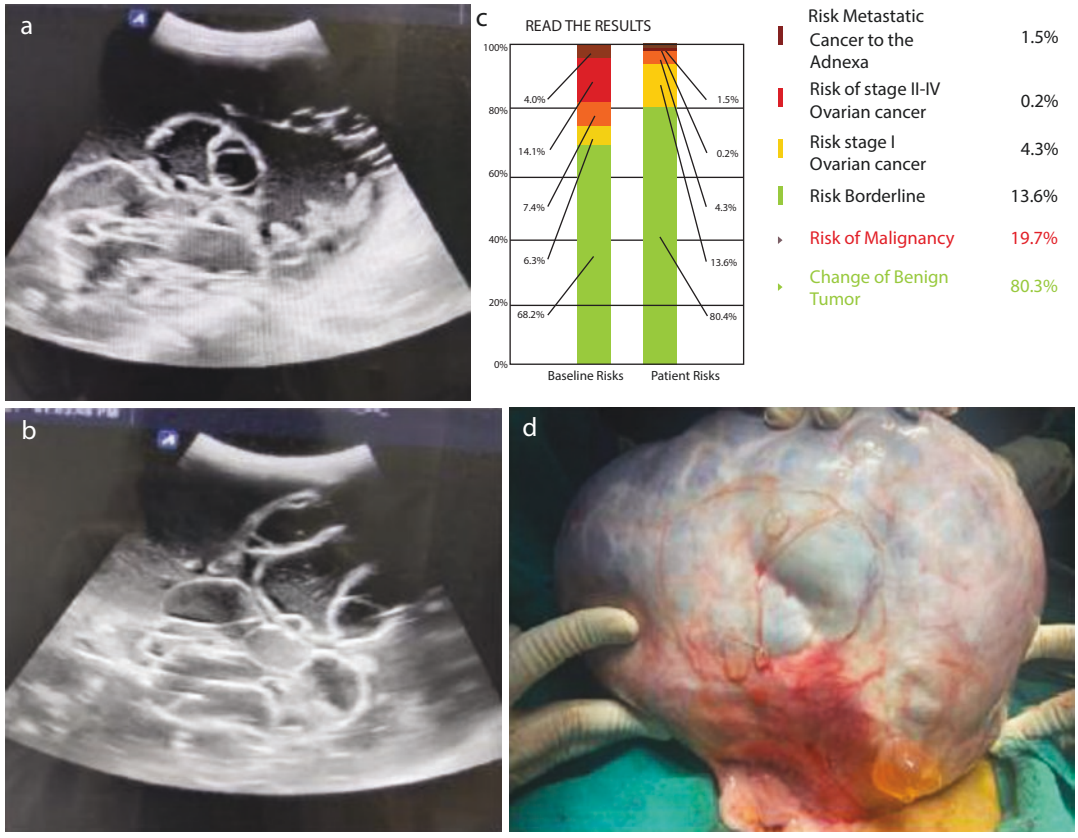


Fig. 1.3 (**a**) Gray scale ultrasound image showing low level of internal echogenicity. (**b**) Gray scale ultrasound showing image of multiloculated cyst with numerous thin septations. Different locules filled with fluid with various degrees of echogenicity. (**c**) ADNEX model- Benign (80.3%), risk of malignancy-19.7%. (**d**). Gross specimen smooth outer surface with cystic appearance, capsule intact. **Final histopathology- Mucinous cystadenoma**

Q: What Are the Basic Principles of Surgical Staging in Adnexal Masses and What Are the Special Considerations for Mucinous Tumours?

Surgical staging for suspected ovarian masses includes peritoneal cytology, systematic comprehensive evaluation of the pelvis and abdomen followed by surgical procedures with commonly include total hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, sampling of any suspicious areas and peritoneal biopsies. In young women like the above case, fertility preservation should be considered in which the uterus and contralateral normal ovary can be left. Systematic lymphadenectomy is considered for early stage non mucinous epithelial cancers as a part of surgical staging. Care should be taken to remove the involved ovary intact without spillage of the contents, as rupture of a stage I disease may increase its potential for recurrence and surgical spill increase the stage to 1C1.

In mucinous ovarian tumor, close inspection of the upper and lower gastrointestinal tract including appendix should always be performed as primary mOC are relatively rare. Current evidence support not performing a routine appendectomy for mucinous tumors as long as the appendix appears normal and there is no evidence of pseudomyxoma peritonei.

If the tumor appears to be widespread, the surgeon should determine whether the disseminated disease is resectable, preferably to no gross residual disease (R0 resection) or R1 where size of the residual disease is <1 cm. If this is possible, then every effort should be made for maximal debulking surgery. If total gross surgical resection is not possible, then consideration should be given to alleviating patient symptoms, e.g., bowel resection for an impending obstruction, and stopping the procedure in favor of chemotherapy.

Sampling of the pelvic and para-aortic lymph nodes is not recommended in mucinous tumours as incidence of nodal metastases in these patients is <1%. Any enlarged lymph node, however, should be sampled.

Q: Role of Minimally Invasive Surgery in Adnexal Masses?

Minimally invasive surgery is being increasingly used for management of adenexal mases. The specimen should be removed intact without spillage of contents in peritoneal cavity. Once the mass is detached, it should be placed into an intraperitoneal specimen bag, and the edges of the bag drawn up through one abdominal incision, which can be enlarged. In smaller masses it is drained outside with needle and syringe or with a suction device without risking peritoneal contamination. Morcellation in the peritoneal cavity or contamination of the trocar sites should be absolutely avoided. The port sites can be washed with saline at the end of procedure. Thorough intraperitoneal lavage should be done at the end of the procedure. If intraperitoneal spill is deemed likely, the surgeon should immediately convert to a laparotomy.

Key Points

- Adnexal masses may be physiological or pathological
- Transvaginal ultrasonography is the first line imaging investigation to characterize an adnexal mass into possibly benign or malignant.
- The IOTA simple rules and ORADS are two classification systems for adnexal masses on imaging
- Risk of malignancy is determined based on USG imaging along with relevant history and serum biomarkers. Various triaging models like Risk of malignancy index, ADNEX model and ORADS can be used to triage masses to be referred to gynae oncologist.

References

1. Palvik EJ, Ueland FR, Miller RW, Ubellacker JM, DeSimone CP, Elder J, et al. Frequency and disposition of ovarian abnormalities followed with serial transvaginal ultrasonography. Obstet Gynecol. 2013;122:210.

2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25:1329.
3. Kauff ND, Mitra N, Robson ME, et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. J Natl Cancer Inst. 2005;97:1382.
4. Koornstra JJ, Mourits MJ, Sijmons RH, et al. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol. 2009;10:400.
5. Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clin Genet. 2009;75:141.
6. Ramus SJ, Song H, Dicks E, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. J Natl Cancer Inst. 2015;107:djv214.
7. Song H, Dicks E, Ramus SJ, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. J Clin Oncol. 2015;33:2901.
8. Lee JS, John EM, McGuire V, et al. Breast and ovarian cancer in relatives of cancer patients, with and without BRCA mutations. Cancer Epidemiol Biomarkers Prev. 2006;15:359.
9. Ness RB, Cramer DW, Goodman MT, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2002;155:217.
10. Kim MK, Kim K, Kim SM, Kim JW, Park NH, Song YS, Kang SB. A hospital-based case-control study of identifying ovarian cancer using symptom index. J Gynecol Oncol. 2009;20(4):238–42.
11. Lataifeh I, Marsden DE, Robertson G, Gebski V, Hacker NF. Presenting symptoms of epithelial ovarian cancer. Aust N Z J Obstet Gynaecol. 2005;45(3):211–4.
12. Kaijser J, Vandecaveye V, Deroose CM, et al. Imaging techniques for the pre-surgical diagnosis of adnexal tumours. Best Pract Res Clin Obstet Gynaecol. 2014;28:683–95.
13. Valentin L, Hagen B, Tingulstad S, et al. Comparison of 'pattern recognition' and logistic regression models for discrimination between benign and malignant pelvic masses: a prospective cross validation. Ultrasound Obstet Gynecol. 2001;18:357–65.
14. Timmerman D. The use of mathematical models to evaluate pelvic masses; can they beat an expert operator? Best Pract Res Clin Obstet Gynaecol. 2004;18:91–104.
15. Meys EMJ, Kaijser J, Kruitwagen RFPM, et al. Subjective assessment versus ultrasound models to diagnose ovarian cancer: a systematic review and meta-analysis. Eur J Cancer. 2016;58:17–29.
16. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol. 2008;31:681–90.
17. Timmerman D, Ameye L, Fischerova D, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839.
18. Alcazar JL, Pascual MA, Olartecoechea B, et al. IOTA simple rules for discriminating between benign and malignant adnexal masses:prospective external validation. Ultrasound Obstet Gynecol. 2013;42:467–71.
19. Tantipalakorn C, Wanapirak C, Khunamornpong S, et al. IOTA simple rules in differentiating between benign and malignant ovarian tumors. Asian Pac J Cancer Prev. 2014;15:5123–6.
20. Nunes N, Ambler G, Foo X, et al. Use of IOTA simple rules for diagnosis of ovarian cancer: meta-analysis. Ultrasound Obstet Gynecol. 2014;44:503–14.
21. Kaijser J, Sayasneh A, Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, et al. Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis. Hum Reprod Update. 2014;20:449–62.
22. Basha MA, Metwally MI, Gamil SA, Khater HM, Aly SA, et al. Comparison of ORADS, GIRADS, IOTA simple rules regarding malignancy rate, validity and reliability for diagnosis of adnexal masses. Eur Radiol. 2021;31(2):674.
23. Berek JS, Hacker NF. Berek and hacker's gynecologic oncology. 6th ed. Philadelphia: Wolters Kluwers; 2015.
24. Zanagnolo V, Pasinetti B, Sartori E. clinical review of 63 cases of sex cord tumours. Eur J Gynecol Oncol. 2004;25(4):431.
25. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol. 2003;21(6):1180.
26. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multimarker bioassay utilizing HE4 and CA125 for prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2009;112:40.
27. Plotti F, Guzzo F, Schiro T, Terranova C, et al. Role of human epididymis protein (HE4) in detecting reoccurrence in CA125 negative ovarian cancer patients. Int J Gynecol Cancer. 2019.
28. Canney PA, Wilkinson PM, James RD, Moore M. CA19-9 as a marker for ovarian cancer: alone and in comparison with CA125. Br J Cancer. 1985;52:131.
29. Coleman RL, Herzog TJ, Chan DW, Munroe DG, Pappas TC, Smith A, et al. Validation of a second generation multivariate index assay for malignancy risk of adnexal masses. Am J Obstet Gynecol. 2016;215:82.
30. Musto A, Rampin L, Nanni C, Marzola MC, Fanti S, Rubello D. Present and future of PET and PET/CT in gynecologic malignancies. Eur J Radiol. 2011;78(1):12.
31. Sorensen SS, Mosgaard BJ. Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis. Dan Med Bull. 2011;58(11):A4331.
32. Andreotti RF, Timmerman D, Benacerraf BR, et al. Ovarian-adnexal reporting lexicon for ultrasound: a white paper of the ACR Ovarian- Adnexal Reporting and Data System Committee. J Am Coll Radiol. 2018;15:1415–29.

33. Erratum. J Am Coll Radiol. 2019;16:403–406. https://doi.org/10.1016/j.jacr.2019.01.011.
34. Andreotti RF, Timmerman D, Strachowski LM, et al. O-RADS US risk stratification and management system: a consensus guideline from the ACR Ovarian-Adnexal Reporting and Data System Committee. Radiology. 2020;294:168–85.
35. Basha MAA, Metwally MI, Gamil SA, et al. Comparison of O-RADS, GI-RADS, and IOTA Simple Rules regarding malignancy rate, validity, and reliability for diagnosis of adnexal masses. Eur Radiol. 2021;31:674–84.
36. Van Calster B, Van Hoorde K, Valentin L, Testa AC, Fischerova D, Van Holsbeke C, et al. evaluating the risk of ovarian cancer before surgery using ADNEX model to differentiate between benign, borderline, early and advanced stage II-IV invasive and secondary metastatic ovarian tumours: prospective multicentre diagnostic study. BMJ. 2014;349:g5920.
37. Querleu D, Planchamp F, Chiva L, et al. European Society of Gynaecological Oncology (ESGO) guidelines for ovarian cancer surgery. Int J Gynecol Cancer. 2017;27:1534–42.

Epithelial Ovarian Cancer: High Grade Serous

2

Bindiya Gupta

Introduction

Ovarian cancer mainly presents in the advanced stage (70%) when tumor has spread to the peritoneal cavity and other abdominal organs. Five -year survival in these advanced stages have always been dismal not more than 50% [1]. The risk factors for epithelial ovarian cancers include increasing age, infertility, endometriosis, polycystic ovarian syndrome and cigarette smoking, personal or family history of hereditary ovarian and breast cancer syndromes [2]. Genetic screening is recommended in all cases of newly diagnosed non mucinous epithelial ovarian cancer.

However, in the recent years, treatment has been revolutionized by changes in surgical and medical management, introduction of targeted therapies and biomarker directed therapies. This change in the treatment paradigm has had substantially improved survival statistics.

In this chapter we will discuss several case scenarios regarding epithelial ovarian cancer.

Case 1: Early Stage Epithelial Ovarian Cancer

Age, Parity, PS	74/F, Nulliparous, PS-1
Clinical presentation	Complaints of leg swelling, incidental diagnosis of ovarian mass Appetite normal, no weight loss Weight: 39 kg, BMI: 19 Abdominal examination: 18 weeks size mass arising from pelvis
CECT chest abdomen and pelvis (Fig. 2.1a, b)	Left adnexal complex cyst 12.5 × 13.2 × 12.4 cm, with irregular solid nodules and septations. Horse shoe kidney. Uterus normal. No retroperitoneal lymph nodes. Upper abdomen normal. No ascites
Co-morbidities	Hypertension, osteogenesis imperfecta
Other investigations	CA125: 836 u/ml, CEA: 5.2 ng/ml Albumin 43 g/L
Management	Primary debulking surgery (R0): Total abdominal hysterectomy, bilateral salpingo oophorectomy+ total omentectomy
Histology	High grade serous cancer involving left fallopian tube, ovarian capsular involvement. Peritoneal cytology negative. Omentum normal P53 null phenotype, WT1 positive, ER 6/8, PR negative

B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_2

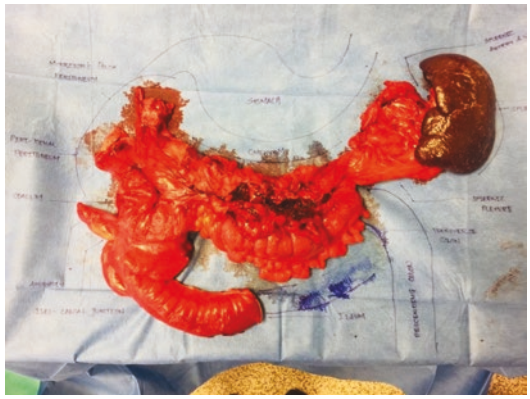


Fig. 2.1 Showing en-bloc debulking with splenectomy, omentectomy and extended right hemicolectomy

Q: What Further Investigations Would You Like To Do for Work Up of Ovarian Cancer?

A preliminary clinical evaluation should include general assessment of the patient surgical fitness including age, functional status (performance score), co morbidities, nutritional status including hemoglobin, serum albumin, liver kidney function tests and X ray chest.

Assessment of disease includes a computed tomography of chest, abdomen and pelvis to evaluate the extent of disease and feasibility of surgical resection. The presence of lung metastasis (>7 mm), pleural effusion, deposits on the large-bowel mesentery (>10 mm) and small-bowel mesentery (>10 mm), and infrarenal para-aortic nodes significantly predict suboptimal debulking *with* sensitivity of 69.2%, specificity of 71.4%, positive predictive value of 75.0% and negative predictive value of 65.2% [3]. In a recent Cochrane meta analysis for abdominal CT, the sensitivity for assessing incomplete debulking was 0.66 (95% CI 0.52 to 0.78) and the specificity 0.77 (95% CI 0.63 to 0.87) [3]. Retrospective data have shown that CT cannot accurately predict fine nodule peritoneal carcinomatosis, and therefore mitigate against suboptimal cytoreduction, and that it is not always reliable and reproducible.

Tumor markers like CA125, CEA, CA125/CEA ratio, CA19.9 are important to ascertain primary ovarian malignancy.

In some cases, additional imaging modalities like whole body diffusion weighted MRI (WB-DWI/MRI) and/or positron emission tomography have also been suggested to be useful in evaluating the extent of disease. Diagnostic laparoscopy is also an option for patients with questionable resectability to assess tumor distribution and predict optimal surgical resection. It is also an opportunity to collect tissue for histopathologic confirmation.

Q: What Is the Treatment of Choice for HGSOC?

Primary debulking surgery followed by adjuvant chemotherapy is the standard of care. It allows for accurate FIGO staging and the aim should be to achieve complete cyto reduction (CC0). In cases where there is a high risk of perioperative morbidity and inability to achieve complete/optimal cytoreduction at primary cytoreductive surgery due to extensive disease, neo adjuvant chemotherapy is offered (discussed in case 2). The choice of operating team is of paramount importance in ensuring a good oncologic outcome. The surgery should be performed by an experienced team and at an established gyneoncology centre with a high case load, experienced surgeons, anesthetists and support staff.

The Society of Gynecologic Oncology and American society of Clinical Oncology clinical practice guidelines have stated that primary cytoreduction is indicated for those women who have high likelihood for achieving residual disease (<1 cm) preferable no residual disease with acceptable morbidity [4]. Removal of large tumours that are poorly vascularized helps to remove pharmacologic sanctuaries and allow for optimal killing of cells that are better perfused and prevent chemo-resistance.

Surgery for apparent early stage ovarian cancer consists of peritoneal washings/ascitic sam-

pling taken prior to manipulation of the tumour, bilateral salpingo-oophorectomy, total hysterectomy, multiple peritoneal biopsies from the paracolic spaces, and the sub-diaphragmatic spaces bilaterally, omentectomy, with bilateral pelvic and para-aortic lymph node assessment up to the level of the insertion of the ovarian vessels in the absence of peritoneal dissemination [5]. Full surgical staging provides useful prognostic information and depending on the histological grade and subtype, up to 30% of the patients with apparently early epithelial ovarian cancer will be upstaged after comprehensive surgical staging.

In advanced stages, only bulky nodes should be removed and systematic lymphadenectomy does not give a survival advantage [6]. Other debulking procedures that may be required include multi-visceral resection such as peritoneal stripping, diaphragmatic resection, splenectomy, liver and/or liver capsule resection and bowel resection. In a recent study at Memorial Sloan Kettering, the feasibility, safety and survival outcomes of intrathoracic surgery was investigated in 178 patients as a part of primary cytoreduction. Among all patients, the median PFS was 33.6 months (95% CI: 24.7–61.9) and the 3-year PFS rate was 48.9% (95% CI: 41.2%–56.2%). Median OS was 81.3 months (95% CI: 68.9–103). When stratified by residual disease status, median PFS was 51.8 months when CGR was achieved versus 16.7 months with residual disease (HR: 2.17; $P < 0.001$) and median OS was 97.6 months when CGR (complete gross resection) was achieved versus 65.9 months with residual disease (HR: 2.05; $P = 0.003$) [7].

Maximal effort should be made to remove all gross disease in abdomen, pelvis and retroperitoneum. The volume of residual disease correlated with survival i.e. with each 10% increase in maximal cytoreduction, a 5.5% increase in median survival time was seen [8]. Studies have shown that median overall survival in relation to residual disease is 106 months with no gross residual; 66 months (gross ≤0.5 cm); 48 months (0.6–1.0 cm); 33 months (1–2 cm) and 34 months (>2 cm) [9]. Figures 2.1–2.4 indicates various surgical procedures to ensure complete cytoreduction.

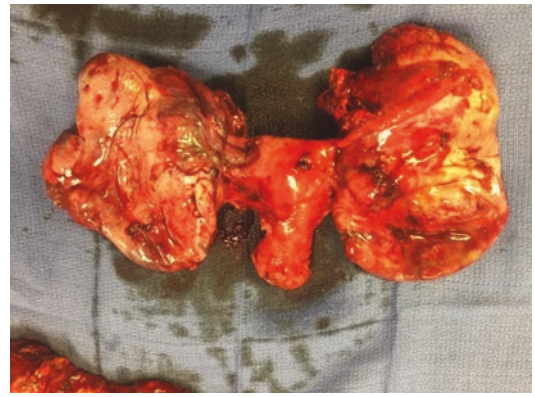


Fig. 2.2 Uterus with bilateral ovarian tumours

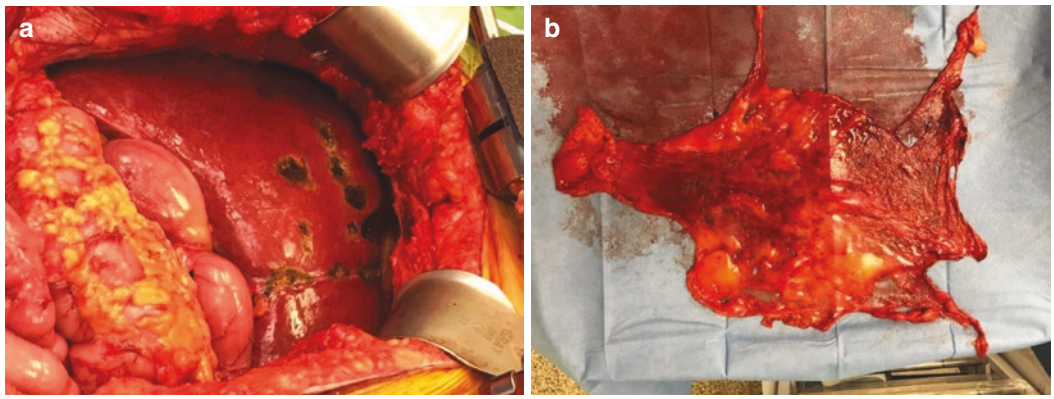


Fig. 2.3 (**a**) Liver with superficial deposits removed (**b**) diaphragm stripped

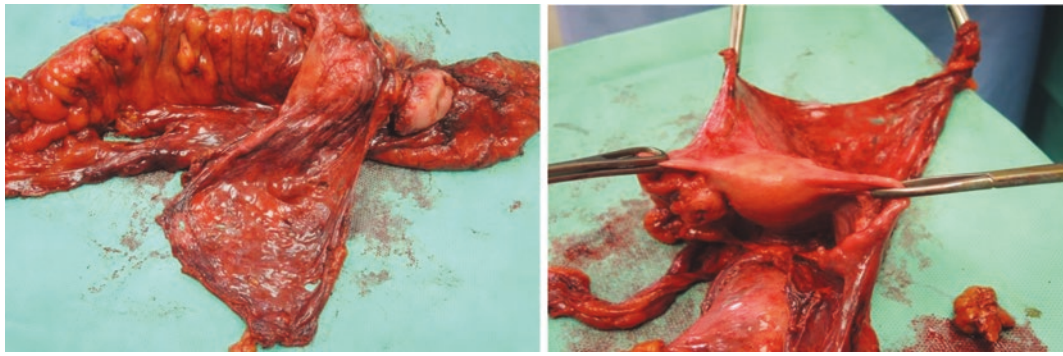


Fig. 2.4 Modified posterior exenteration with total pelvic peritonectomy

Table 2.1 Alleti Surgical complexity scoring system based upon complexity and number of surgical procedures performed

Procedure	Points
TH-BSO (total hysterectomy +bilateral salpingo-oophorectomy)	1
Omentectomy	1
Pelvic lymphadenectomy	1
Paraaortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Rectosigmoidectomy_T-T anastomosis	3
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection/s	2
Small bowel resection/s	1

To explore the association between extent of cytoreductive surgery, acute morbidity, and overall survival, Aletti et al. constructed a novel surgical scoring system i.e. the surgical complexity score (SCS) [10]. The score has assigned a numeric value to each procedure performed during PDS based on the inherent difficulty of the case (Table 2.1). Less than 3 is low score, intermediate 4–7 and high 8 or more. Higher SCS i.e. more complex surgery benefits with increased overall survival rate with lower residual disease. Risk of complication rates increases with higher score and associated cofactors but this did not translate into mortality.

Q: Role of Lymphadenectomy in Ovarian Cancer?

The role of lymphadenectomy in ovarian cancer is debatable. The proponents of lymphadenectomy suggest that routine lymphadenectomy helps to surgically remove micro-metastasis and hence all neoplastic foci; on the other hand, some surgeons argue that it does not have any impact of survival, increases morbidity and preserving lymphatic tissue spares the immune system.

Early stage ovarian cancer: The incidence of nodal metastasis in early ovarian cancer is around 14.2% out of which 7.5% are in the paraaortic nodes, 3.6% in pelvic nodes, 4.3% in both pelvic and paraaortic nodes [11, 12]. The highest incidence of lymph node metastasis has been found in the serous subtype (23%) and lowest in mucinous subtype (2.6%). The benefit of lymphadenectomy in early stage ovarian cancer is for the purpose of staging and deciding adjuvant treatment. No first level evidence suggests overall survival benefit of lymphadenectomy in early stages (84% versus 81.6%) [13]. In fact, retroperitoneal staging is related with a higher incidence of surgery related morbidity and prolonged post operative stay.

Retroperitoneal staging is useful to identify the 15% of early stage EOC who will require adjuvant chemotherapy. Detection of nodal metastasis on PET CT scan has a sensitivity of

around 70%, hence in two third of these patients, lymph node metastasis can be detected on PET –CT in early stage disease, thereby avoiding complete lymphadenectomy in this group. Trials are also underway to detect sentinel nodes in ovarian cancer, and preliminary results have shown a detection of 67% in para aortic and paracaval regions, 9% in pelvic region only and both areas 24% [14]. There is increasing evidence that occurrence of isolated nodal recurrences can be safely treated with rescue surgery. There is no role of lymphadenectomy in mucinous cancers.

Patients should be carefully counseled, choice of performing this procedure should be analyzed and discussed with each patient.

Advanced stage: In advanced stages it has been demonstratedin randomized trials that only removal of bulky nodes should be a part of surgical debulking to achieve complete cytoreduction. Routine lymphadenectomy is not associated with better outcomes and in fact has higher complication and mortality rate [15, 16].

Q: How Do You Assess Intraoperatively the Spread of Disease in Abdomen?

Intraoperative disease burden can be assessed by an objective score known as peritoneal cancer index (PCI) which was first described in 1996, by Sugarbaker PH et al. [17]. It is used to assess cancer distribution in peritoneum quantitatively by calculating tumor size in 13 abdominopelvic regions. It provides valuable information about exact distribution and tumor volume including details of extent of peritoneal spread. PCI score > 10 is considered poor prognostic factorand disease free survival is poor with PCI > 15 [18]. Lower the PCI, the higher the likelihood of achieving CCS 0. For a PCI of 5, the probability of achieving CCS 0 was at 77.7% while for a PCI of 15, it was only 38.6% [19].

Q: Role of Adjuvant Treatment Post Surgery in Early and Advanced Ovarian Cancer

The decision for adjuvant therapy should be individualized according to stage, histology, resection and adequacy of staging, co morbidities and presence of drug allergy.

Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of ovarian cancer apart from low grade stage Ia/Ib [5]. The first line treatment consists of Paclitaxel and carboplatin (AUC 5) three weekly for 6 cycles. Carboplatin is less toxic than cisplatin and equally effective. The standard of care is three-weekly carboplatin (AUC5/6) and paclitaxel (175 mg/m^2) for six cycles.

ICON1 trials demonstrated a significant improvement in both relapse-free survival (RFS) (Hazard Ratio (HR) = 0.65, 95%CI = 0.46–0.91, p = 0.01) and overall survival (OS) (HR = 0.66,95%CI = 0.45–0.97, p = 0.03) in favour of adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6) [20]. ACTION trial further showed that patients who received platinum-based adjuvant chemotherapy had a better OS (hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment [21]. Use of dose dense therapy does not improve PFS compared to three weekly regimen [22].

Q: Role of Anti-angiogenic Treatment in EOC Upfront Setting

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Toxicity includes hypertension, proteinuria, hemorrhage, thrombosis and bowel perforation. Modest benefit in PFS of 4 months have been shown in the ICON 7 and GOG 218 trials and there was no overall survival benefit [23]. However, in a subset analysis of ICON 7 who had

poor prognosis (Stage 4, inoperable stage 3, sub optimally debulked stage 3) it was associated with an OS advantage of 4.5 months (p = 0.03) [24]. Use of bevacizumab must be individualized in upfront settings.

Q: Role of HIPEC in Ovarian Cancer

Hyperthermic intraperitoneal chemotherapymeans intraoperative delivery of heated intraperitoneal chemotherapy after achieving optimal cytoreduction. Hyperthermia is cytotoxic in itself as well as increases the chemo penetration in the tissues.

The main concerns regarding the use of HIEPC in ovarian cancer are the prolonged operative time, potential toxicity, and postoperative morbidity from HIPEC. Another concern is that there should not be any delay in the initiation of post operative adjuvant chemotherapy.

van Driel (2018) in a phase III randomized controlled trial administered HIPEC (100 mg/m^2 of cisplatin for 90 min at 40 degree celsius) in patients with FIGO stage III EOC who had received NACT [25]. The HIPEC group showed significantly better PFS (median, 14.2 versus 10.7 months; HR, 0.66;) and OS (median, 45.7 versus 33.9 months; HR, 0.67;) than the control group with similar toxicity profile as that of control group. Italian and Korean real-world studies have shown that HIPEC at the time of interval CRS is feasible, without an increase in the rate of complications or deterioration in the patient's condition after surgery [26–28]. An ongoing phase III RCT, OVHIPEC-2, will investigate whether the addition of HIPEC to primary CRS would improve the survival outcomes. Role of HIPEC in recurrent disease is also not yet proven.

According to the National Comprehensive Cancer Network guidelines, HIPEC with 100 mg/m^2 of cisplatin can be considered during interval CRS for FIGO stage III disease. Sodium thiosulfate may be administered at the start of perfusion, followed by a continuous infusion, to allow for renal protection during HIPEC [29].

Case 2: Stage 4A

Age, Parity, PS	71 /F, P1 + 0, PS-1
Clinical presentation	Known case of high grade serous ovarian cancer stage 4 A ((malignant pleural effusion) CECT: Image guided biopsy from omental cake: High grade serous carcinoma Ovary (CK 7, PAX 8 positive, p53 aberrant) Neoadjuvant chemotherapy: 4 cycles (carboplatin + paclitaxel)
CECT chest abdomen and pelvis	Resolution of pleural effusion, ascites, reduction in omental cake and ovarian mass sizes with resolution of subcapsular liver disease and, reduction in size of paraaortic node
Co-morbidities	Hypertension, Ischaemic heart disease (had stent insertion 2018)
Other investigations	CA-125 reduced from 1464 IU/ml to 12 IU/ml
Management	Delayed debulking surgery: supra colic omentectomy, bilateral salpingoophorectomy +total abdominal hysterectomy+ removal of enlarged para aortic nodes (4 cm) + anterior bladder peritonectomy (R0 resection)
Histology	High grade serous cancer of fallopian tube involving ovary, omentum,left paracolic peritoneum positive, paraaortic lymph node positive CRS 2 P53 aberrant, PAX 8, WT-1 positive, CK 20 negative, PR negative, ER weak

Q: What Is the Selection Criteria for NACT and What Are the Predictors of Inoperability?

Two main factors taken into consideration when deciding for mode of treatment (primary debulking or NACT) are the ***risk of high perioperative morbidity*** and ***ability to achieve complete /optimal cytoreduction at primary cytoreductive surgery***. If R0 is difficult to attain at primary cytoreduction, neoadjuvant chemotherapy followed by delayed debulking surgery is the treatment of choice. Neoadjuvant chemotherapy also offers the opportunity for in vivo chemosensitivity testing.

Neoadjuvant Chemotherapy Can Be Given Under Following Conditions:

1. Factors associated with increased morbidity include advanced age (≥75 years), poor performance status, newly diagnosed venous thromboembolism, multiple co morbidities, ASA score of 3 or 4, low albumin (<3.0 g/dL), a higher surgical complexity score, and stage IV disease (lung, mediastinum and brain metastasis, multiple liver parenchymal metastasis) making the patient unfit for primary surgery.
2. Disseminated high volume disease with involvement of small bowel, bulky porta hepatis disease, involvement of coeliac trunk, mesenteric infiltration or retraction or nonresectable extra abdominal lymph nodes (retrocrural or suprarenal retroperitoneal nodes) [30].
3. Cytoreduction is likely to compromise visceral function e.g. multiple bowel resections.
4. Faggoti Score on laparoscopy (Table 2.2) [31]: Faggotti et al. proposed a score with a Predictive index value (PIV) to determine complete cytoreduction. The total score calculated is a score to predict the surgical outcome and higher is the PIV more the likelihood of having a suboptimal surgical result (PPV) being 100% with a PIV ≥8.

Q: Briefly Describe the Protocol of Neoadjuvant Chemotherapy?

Before starting chemotherapy there should be a biopsy proven diagnosis of invasive ovarian, fallopian tube or primary peritoneal cancer. However, when a biopsy cannot be performed, a cell block may be made from ascitic fluid to confirm the presence of malignancy and immunohistochemistry markers can confirm adenocarcinoma of ovarian origin.

Neoadjuvant chemotherapy (NACT) consists of 3–4 cycles of a platinum/taxane doublet; carboplatin (AUC = 5) and paclitaxel (175 mg/m^2) every 3 weeks. Interval debulking surgery (IDS), also called delayed debulking surgery (DDS) or interval cytoreduction (IC) should be performed within 4 weeks of completion of the last cycle of chemotherapy for women with response to chemotherapy or stable disease [32]. Within 4 weeks of surgery, four more cycles of adjuvant chemotherapy are administered. Bevacizumab containing regimens for NACT should be used with cautionas it may

Table 2.2 Faggoti score on laparoscopy

Laparoscopic feature	Score 0	Score 2
Peritoneal carcinomatosis	Carcinomatosis involving a limited area (along the paracolic gutter or the pelvic peritoneum) and surgically removable by peritonectomy	Unresectable massive peritoneal involvement as well as with a miliary pattern of distribution
Diaphragmatic disease	No infiltrating carcinomatosis and no nodules confluent with the most part of the diaphragmatic surface	Widespread infiltrating carcinomatosis or nodules confluent with the most part of the diaphragmatic surface
Mesenteric disease	No large infiltrating nodules and no involvement of the root of the mesentery as would be indicated by limited movement of the various intestinal segments	Large infiltrating nodules or involvement of the root of the mesentery indicated by limited movement of the various intestinal segments
Omental disease	No tumor diffusion observed along the omentum up to the large stomach curvature	Tumor diffusion observed along the omentum up to the large stomach curvature
Bowel infiltration	No bowel resection was assumed and no miliary carcinomatosis on the ansae observed	Bowel resection assumed or miliary carcinomatosis on the ansae observed
Stomach infiltration	No obvious neoplastic involvement of the gastric wall	Obvious neoplastic involvement of the gastric wall
Liver metastases	No surface lesions	Any surface lesion

compromise post operative healing and increase hemorrhagic complications. It should be withheld from therapy for at least 28 days before DDS [33].

Q: What Are the Parameters that Can Be Used for Evaluation of Response to NACT?

There are no definite criteria available to predict an accurate response; however certain parameters are used to have a fair idea of chemotherapy response. Clinical response to therapy may be evaluated by symptomatic improvement, resolution of ascites and decrease in size of masses. CA125 levels should be measured after each cycle of chemotherapy and decrease in CA-125 levels is correlated with good response to NACT in several studies. Normalization of CA-125 prior to IDS is also associated with improved survival.

CT scan of chest, abdomen and pelvis should be done after the third cycle to assess response. The RECIST 1.1 criteria for solid tumors has been used to assess chemotherapy response on CT scan in few studies [34]. **Complete response** was taken as disappearance of all non-nodal target lesions and any reduction in short axis to <10 mm for nodal targets. **Partial response** was at least a 30% decrease in the sum of diameters of all lesions compared to baseline while **Progressive disease** is at least 20% increase in the sum of diameters of all measured target lesions, compared to the smallest sum recorded at or after baseline. **Stable disease** is neither sufficient shrinkage or increase in lesion size. The surgical resection was incomplete with stable and progressive disease; however, the data was retrospective and there is a need for more prospective studies.

The histologic response to neoadjuvant chemotherapy can be made using the Chemotherapy response score (CRS). This is a validated and standardized three-tier scoring system for histological tumor regression in tubo-ovarian HGSC and yields prognostic information [35]. It stratifies patients into complete/near-complete (CRS3), partial (CRS2), and no/minimal (CRS1) response based on omental examination [36]. CRS3 is associated with good prognosis.

It has also been shown that carriers of BRCA germline mutations and six other genes of the homologous recombination pathway have a better response to chemotherapy.

Q: What Parameters Should Be Considered for Deciding Surgery After NACT?

The aim of delayed debulking surgery (DDS) is to achieve complete cytoreduction or R0. Optimal cytoreduction (residual disease <1 cm) The decision to perform surgery after 3–4 cycles of neoadjuvant chemotherapy can be made on the basis of the following conditions:

(a) **Response to NACT:** The response to chemotherapy prior to surgery is assessed as described as above. In cases where there is a ***complete response*** surgery is performed within 4 weeks of completion of the last cycle of chemotherapy. In cases of ***partial response*** surgery may be considered and a diagnostic laparoscopy can be performed to assess operability based on surgeon's discretion. Alternatively, initially a smaller incision is made during laparotomy for DDS to assess disease spread which later is increased if the surgeon decides to proceed further. In cases of ***progressive disease*** suggesting a possible platinum resistance or refractoriness patient-should not be operated unless for palliative reasons like bowel obstruction etc. that cannot be managed conservatively. Options include alternative chemotherapy regimens (gemcitabine, pegylated liposomal doxorubicin, or bevacizumab), clinical trials, and/or discontinuation of active cancer therapy and initiation of end-of-life care. BRCA testing (somatic and germline) should be offered and PARP inhibitors can be considered.

(b) **WHO performance status, serum albumin levels and co morbidities:** WHO performance status of 0 or 1 and a serum albumin of >30 g/l is preferable to ensure better outcomes after surgery. Presence of multiple co-morbidities like acute pulmonary embolism, heart failure etc. increase the risk of surgery and continuation of chemotherapy may be considered in these patients.

Q: What Is the Available Evidence to Support NACT? How Should This Information Guide Initial Treatment?

Four major randomized trials have been conducted comparing NACT-IDS with primary debulking surgery (PDS) and the results are summarized in Table 2.3. In a pooled analysis of EORTC and CHORUS trials of 1220 women

Table 2.3 Randomized clinical trials comparing NACT-IDS with PDS + adjuvant chemotherapy

Trial name stage, no of patients (n)	Complete cytoreduction (%) RD: 0 mm (NACT-IDS versus PDS)	Complications	PFS (median) (NACT-IDS versus PDS)	OS (median) (NACT-IDS versus PDS)	Comments
EORTC 55971 trial [37] (EORTC+ NCIC initiated) Vergote et al. 2010 Stage IIIC-IV N = 668	51.2 versus 19.4	Lower with NACT-IDS	12 months in both arms, (HR, 1.01; 95% CI, 0.86–1.17)	29 vs. 30 months (HR, 0.98; 95% CI, 0.82–1.18)	OS was significantly better in the PDS group with complete and optimal cytoreduction NACT is non inferior to PDS
CHORUS trial [38] Kehoe et al. 2015 Stage III-IV N = 550	39 vs17	Grade 3–4 adverse events more in PDS	11.7 *vs.* 10.3 months	24.1 *vs.* 22.6 months	HR for death was 0.84 (in favour of NACT) Survival with primary chemotherapy before surgery is non-inferior to primary surgery
JCOG0602 [39, 40] trial Onda et al. 2014 III-IV N = 301	64 vs12	NAC arm less blood loss, lower grade 3and 4 adverse events	16.4 vs15	44.3vs 49	NAC arm required fewer surgeries, shorter operating time, fewer abdominal organ resections 1. NAC treatment is less invasive 2. For survival, noninferiority of NACT was not confirmed
SCORPION [41] Fagotti et al. 2016 IIIc-IV N = 110 (Fagotti score 8–12)	57.7 vs 45.5	Grade 3–4 complications significantly less in NACT	–	–	Perioperative moderate/severe morbidity, QoL scores shown to be more favourable in NACT/IDS

EORTC European Organization for Research and Treatment of Cancer (EORTC), *NCIC* National Cancer Institute of Canada, *PDS* Primary debulking surgery, *Adjuvant Chemotherapy* 6 cycles carboplatin and Paclitaxel, *NACT* Neoadjuvant chemotherapy (carboplatin and paclitaxel for three cycles), *IDS* Interval debulking surgery, *PFS* Progression free survival, *OS* Overall survival, *RD* gross residual disease, *CHORUS* The CHemotherapy OR Upfront Surgery (CHORUS)

after a median follow up of 7.6 years, overall survival (OS) was similar in both groups (26.9 months in PDS versus 27.6 months with NACT) [42]. In a subgroup analysis, there was a 3 months' survival advantage with NACT in stage IV disease while OS was better with upfront debulking surgery in patients with IIIc disease with complete cytoreduction and extra pelvic metastasis <5 cm.

A recent meta-analysis (2018) concluded that NACT/IDS could improve the rate of optimal debulking and decrease post-operative adverse events. However, to ascertain a survival advantage more randomized trials are needed. Another trial TRUST is underway in which quality assurance is added in the PDS arm by ensuring at least 50% complete cytoreduction in these group of patients.

Until more evidence is available, factors such as patient characteristics, tumor load, disease resectability scores, surgeon and patient preferences and resource availability will help to guide management. NACT can be offered when the patient is at high risk of perioperative morbidity or there are chances of incomplete cytoreduction as NACT is non inferior to PDS and is associated with less complications.

Case 4: Ca Ovary with Massive Ascites

Age, Parity, PS	80 year P1 + 0, PS-1
Clinical presentation	Symptoms of abdominal distension, previous hysterectomy with conservation of one ovary, previous cholecystectomy **Examination:** Ascites+
CECT chest abdomen and pelvis	Lungs normal, no lymph nodes, significant ascites with peritoneal thickening in the left upper quadrant, pelvic peritoneum thickened. Omental cake present Signs of chronic liver disease (liver has a nodular contour) No pelvic mass, no retroperitoneal lymphadenopathy
Co-morbidities	Diabetes
Other investigations	Ca125: 195, 228, CA19–9557, CEA =1, Ca15–3: 9(<31ku/l)
Management	**Image guided biopsy:** Chronic inflammation **Ascitic fluid tapping (twice):** Metastatic adenocarcinoma, (ovarian/ endometrial source) WT1 + ve, weak sporadic PAX8, ER + ve, CK20 negative not fitting entirely with mullerian primary **Diagnostic laparoscopy** Laparoscopy +biopsy: peritoneal carcinomatosis, omental cake, left fallopian tube normal 2 l of ascitic fluid drained. Ovaries bulky
Histology	High grade serous ovarian cancer,P53 null phenotype, WT1 positive, ER 6/8, PR negative

Q: Role of Laparoscopy in Management of Ovarian Cancer

Laparoscopy is considered following conditions in ovarian cancer:

(a) **To confirm diagnosis:** In majority of the cases tissue can be safely obtained through image guided biopsy. However, in certain conditions as in ***the present case***, when biopsy was inconclusive and repeated ascitic fluid cytology was inconclusive regarding the primary site, laparoscopy may be considered to obtain pre-treatment histology.

(b) **Assessment of operability**: A diagnostic laparoscopy may be considered to assess resectability in primary debulking surgery when accurate assessment of tumor load cannot be made on imaging, especially in cases with ascites (Fagotti score as in Table 2.1). It can also be used when there is a partial response to NACT to assess whether complete cytoreduction is feasible.

(c) At present, very few studies have been done to establish the role of minimally invasive surgery after NACT. According to the authors in the INTERNATIONAL MISSION study [43], MIS may have a role in low-complexity standard cytoreductive procedures, where disease volume is low. The proposed benefits of MIS in surgery for advanced ovarian cancer surgery include decreased blood loss, shorter hospitalization, rapid recovery and early initiation of adjuvant chemotherapy.

Case 5: Diffuse Retroperitoneal Lymphadenopathy in High Grade Serous Ovarian Cancer

Age, Parity, PS	71 years, P3 + 0, PS-1
Clinical presentation	Complaints of pelvic pain × 4 months No alteration in appetite, weight loss or tiredness, normal bowel habits, no urinary complaints Previous history of hysterectomy done for AUB with ovarian conservation History of 6 cm ovarian cyst 4 years back, CA125 done 6 monthly twice; normal; discharged from follow up No allergies, no medical or surgical co-morbidities
CECT chest abdomen and pelvis (Fig. 2.5a–c)	Thorax: No mediastinal or hilar lymphadenopathy, no pleural effusion, incidental 4 mm non specific nodule in right upper lobe Abdomen and pelvis: Ovarian cyst 6 × 5.8 cm, thickened ovarian cyst walls (persistent with no change from previous scans) No ascites, no peritoneal disease, liver, spleen, gallbladder, pancreas, kidneys, bowel normal Multiple enlarged retroperitoneal lymph nodes largest left Para-aortic node at the level of left renal vein 2 × 2 cm. Prominent interaortocaval and retrocaval nodes. Pelvic lymphadenopathy with prominent common iliac nodes largest on right side 2 × 1.6 cm
Co-morbidities	Hypertension

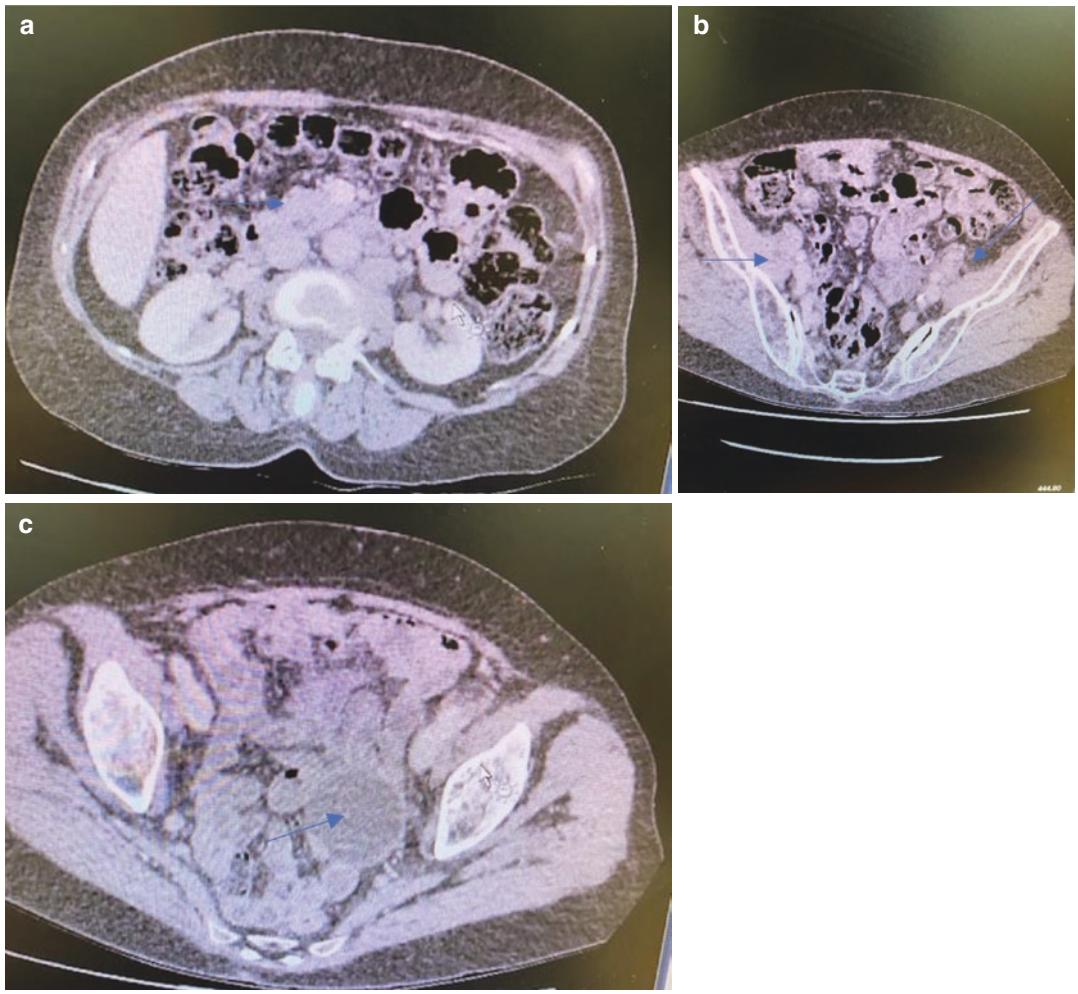


Fig. 2.5 (**a**) CT scan showing paraaotic nodal mass. White arrowhead shows a small suprarenal node above the renal vein. (**b**) Bilateral enlargement of the pelvic nodes. (**c**) Left ovarian mass

CT guided core needle biopsy from left paraaortic node	Metastatic adenocarcinoma IHC: CK7 + VE, CK20-VE ER+, PR +/− PAX 8+, WT1 +, P16 + P53 + ve diffuse and strongly positive (aberrant) Napsin-, GATA3-, CDX2-, CEA-, TTFI-, thyroglobulin -, CA125-, vimentin- Consistent with adenocarcinoma of ovarian serous origin
Other investigations	CA125: 653 KU/L, CEA: 2.5 microgram/L

Q: What Is the Further Management Plan for the Patient?

Patient was counselled and both neoadjuvant and primary debulking options were explained to her.

Recent studies have shown equal tumor regression of primary tumor, peritoneal implants and lymph nodes to chemotherapy. Use of neoadjuvant chemotherapy leads to fibrosis of tumor tissue. Hence, post chemotherapy removal of the nodes becomes difficult due to loss of tissue planes and increased adherence to the nodes to the underlying vessels due to fibrosis. In upfront debulking, tissue dissection is easier due to preservation of the chemotherapy naïve planes; however, a great deal depends on the surgeon's expertise as the amount of nodal mass is of a higher volume and benefits of surgery are only when complete cytoreduction is achieved.

Case was discussed at the multidisciplinary meeting and since patient had no major medical comorbidity, good nutritional status with albumin of 44, no ascites, no visceral infiltration, no gross bowel involvement, and predominantly retroperitoneal disease a decision was made for primary debulking surgery. Nodal mass can also compress on ureter causing renal dysfunction
The patient was counselled regarding its associated benefits, risks and complications and and consent for surgery was taken
Surgery: Primary debulking surgery- bilateral salpingo-oophorectomy + supracolic omentectomy+ pelvic lymphadenectomy and supra renal Para-aortic lymphadenectomy
Intraoperative findings: No ascites, left ovarian mass - 5 cm, right ovary bulky with tumor deposits on surface, Omentum grossly normal, no deposits, minimal adhesions present
Bilateral external iliac and common iliac group of lymph nodes enlarged; nodal mass 4–5 cms on each side, hard in consistency, densely adherent to underlying vessels. Para-aortic group of lymph nodes as a hard conglomerate nodal mass (Para-aortic, interaortocaval, retro-aortic; 8 cm long chain on left side; 5–6 cm nodal mass over the inferior venacava); adherent densely to the adventitia of underlying vessels, psoas major muscle; left paraaortic chain extending supra renal 2 cm, presacral nodal mass-4 cm below the bifurcation
Liver, spleen, diaphragm, pancreas, peritoneum, bowel normal
Histology: High grade serous carcinoma of fallopian tube origin involving both ovaries, FIGO stage IIIA. Omentum tumor free. Metastatic carcinoma in all sampled pelvic and Para-aortic nodes. Left external iliac: 2/2, right pelvic nodes: 9/10, Para aortic nodes: 8/8, suprarenal node 1/1, maximum dimension of largest Para-aortic deposit: 44 mm
Post operative: Patient developed abdominal distension due to ascites 3 weeks post surgery. Underwent paracentesis and 8 l of chylous ascites drained

CT scan can sometimes underestimate the disease as in this case as the nodal disease far more extensive than what was reported by the radiologist. There was also suprarenal vein extension of the lymphadenopathy on left sided para-aortic nodes. CT assessment is also dependent on the reporting radiologist. Maybe the FNA of the node could have also caused the flare up of nodal disease and the operative findings were more extensive than what was anticipated by the CT scan findings. Ideally we aim to have the cross sectional imaging less than 4 weeks prior to major debulking surgery to avoid chances of detecting more than anticipated extensive disease.

Q: What Were the Approaches Used for Para-aortic Lymphadenectomy?

Access to the retroperitoneum is commenced by mobilization of the ascending colon along the white line of Toldt upto the hepatic flexure, with attention to the ureter, right kidney (Cattell -Braasch maneuver). Duodenum is mobilized by incising the peritoneal attachment lateral to the C-shaped curve of duodenum (Kocherization of the duodenum). The peritoneum along the small intestinal mesentery is incised from the ileocaecal junction, passing through the sacral promontory upto the deuodeno jejunal junction. Descending colon also needs to be mobilized on left side till splenic flexure. This facilitates the exposure till renal vein.

For nodes extending above the renal vessels, a retrorenal approach can be adopted. After mobilizing the colon, kidney is mobilized after carefully entering the space between Toldt's fascia and Gerota's fascia, dissecting the descending colon and reflecting the kidney and colon medially and the nodes are accessed from the side.

The surgeon's must be aware of vascular variations during para-aortic lymphadenectomy.

Case 6: BRCA Positive Ovarian Cancer

Age, Parity, PS	48 years, P3 + 0, PS-0
Clinical presentation	Stage 3 ovarian cancer, suspected on USS. Previous history of breast cancer triple negative. Underwent neo adjuvant chemotherapy, mastectomy, axillary node clearance, and radiotherapy 12 years back. BRCA germ line positive
CECT chest abdomen and pelvis	Bilateral solid cystic ovarian masses 5–6 cm. Evidence of peritoneal metastasis with omental caking (24 mm) along the anterior abdominal wall. Small volume ascites. Moderate left sided pleural effusion with atelectasis in left lower lobe
Co-morbidities	Nil
Pleural fluid; ascitic fluid cytology	Positive CK7+, PAX-8 + ve
Other investigations	CA125: 6506; KU/L, CEA: 2.2 microgram/L
Treatment	Received neo adjuvant carboplatin, paclitaxel × 3 cycles Repeat CT scan: Interval response shows resolution of ascites and pleural fluid Right ovarian mass reduced to 2.5 × 1.8 cm; left 3.6 × 2.9 cm Omental cake reduced: 10 mm; no new disease site seen Post chemo CA125: 104 Underwent delayed debulking surgery (R0 resection)
Histopathology	Bilateral high grade serous ovarian carcinoma, omentum positive

Table 2.4 Trial of PARP inhibitors for upfront maintenance in HGSOC

Study	Study arm	Intention to treat analysis	BRCA m	HRD	HRp
PRIMA [46]	Niraparib	HR: 0.62; mPFS: 13.8 vs. 8.2 months	HR 0.40 (0.27–0.62)	HR0.43; mPFS: 21.9 vs. 10.4	HR 0.68 (0.49–0.94)
PAOLA1 [47]	Olaparib + bevacizumab	HR: 0.59 mPFS: 22.1 vs. 16.6 months	HR: 0.31 mPFS: 37 vs. 22 months	HR: 0.33 mPFS: 37 vs. 17.7 months	HR: 0.92 mPFS: 16.9 vs. 16 months
VELIA [48]	Veliparib	HR: 0.68 mPFS: 23.5 vs. 17.3 months	HR: 0.44 mPFS: 34.7 vs. 22 months	–	HR: 0.81 mPFS: 15 vs. 11.5 months

Q: Role of PARP Inhibitors in this Patient

According to the SOLO -1 study, women with BRCA positive advanced HGSOC who achieved complete or partial response to chemotherapy had a hazard ratio of 0.0 and median PFS of 49 months versus 13.8 months with olaparib compared to placebo [44, 45]. US FDA approved Olaparib for use of maintenance following frontline chemotherapy in BRCA associated ovarian cancer. The other key PARP trials for upfront maintenance including PRIMA, PAOLA1 and VELIA are summarized in Table 2.4.

Currently Olaparib and Niraparib (given for 2–3 years) are indicated in frontline ovarian cancer as maintenance for patients with BRCA associated cancer or homologous recombination deficiency status who are in complete or partial remission following chemotherapy. Olaparib can be given in combination with platinum based chemotherapy and bevacizumab [49]. Niraparib can also be used for maintenance therapy regardless of biomarker status [50].

Key Points

1. NACT can be offered when the patient is at high risk of perioperative morbidity or there are chances of incomplete cytoreduction as NACT is non inferior to PDS and is associated with less complications.
2. Indications of NACT include poor performance status, significant medical co morbidities, disseminated high volume disease i.e. with involvement of small bowel, bulky porta hepatis disease, involvement of coeliac trunk, mesenteric infiltration
3. Maximal effort should be made to remove all gross disease in abdomen, pelvis and retroperitoneum and aim of surgery is no gross residual disease
4. Adjuvant treatment consists of consists of Paclitaxel and carboplatin (AUC 5) three weekly for 6 cycles. Use of bevacizumab must be individualized in upfront settings.
5. Routine use of HIPEC has been debatable. It can be used in the interval cytoreduction settings.
6. Olaparib and Niraparib (given for 2–3 years) are indicated in frontline ovarian cancer as maintenance for patients with BRCA associated cancer or homologous recombination deficiency status who are in complete or partial remission following chemotherapy.

References

1. National Cancer Institute. Cancer Stat Facts: Ovarian Cancer. https://seer.cancer.gov/statfacts/html/ovary.html.
2. Kuroki L, Guntupalli SR. Treatment of epithelial ovarian cancer. BMJ. 2020;371:m3773.
3. Borley J, Wilhelm-Benartzi C, Yazbek J, Williamson R, Bharwani N, Stewart V, et al. Radiological predictors of cytoreductive outcomes in patients with advanced ovarian cancer. BJOG. 2015;122(6):843–9.
4. Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of clinical oncology clinical practice guideline. J Clin Oncol. 2016;34:3460–73.

5. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. https://www.bgcs.org.uk/wp-content/uploads/2021/07/BGCS-Ovarian-Guidelines-2017.pdf. Accessed 17 Feb 2023.
6. Harter P, Sehouli J, Lorusso D, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med. 2019;380:822–32. https://doi.org/10.1056/NEJMoa1808424.
7. Kahn RM, McMinn E, Yeoshoua E, Boerner T, Zhou Q, Iasonos A, et al. Intrathoracic surgery as part of primary cytoreduction for advanced ovarian cancer: going to the next level - a memorial Sloan Kettering cancer center study. Gynecol Oncol. 2023;170:46–53.
8. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20:1248–59.
9. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol. 2006;103(2):559–64.
10. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol. 2007;197(6):676.e1–7.
11. Cass I, Li AJ, Runowicz CD, Fields AL, Goldberg GL, Leuchter RS, et al. Pattern of lymph node metastases in clinically unilateral stage I invasive epithelial ovarian carcinomas. Gynecol Oncol. 2001;80(1):56–61.
12. Nomura H, Tsuda H, Susumu N, Fujii T, Banno K, Kataoka F, et al. Lymph node metastasis in grossly apparent stages I and II epithelial ovarian cancer. Int J Gynecol Cancer. 2010;20(3):341–5.
13. Maggioni A, Benedetti Panici P, Dell-Anna T, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer. 2006;95(6):699–704.
14. Kleppe M, Brans B, Van Gorp T, Slangen BF, Kruse AJ, Pooters IN, et al. The detection of sentinel nodes in ovarian cancer: a feasibility study. J Nucl Med. 2014;55(11):1799–804.
15. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med. 2019;380(9):822–32.
16. Benedetti Panici P, Giannini A, Fischetti M, Lecce F, Di Donato V. Lymphadenectomy in ovarian cancer: is it still justified? Curr Oncol Rep. 2020;22(3):22.
17. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Peritoneal carcinomatosis: principles of management. Cancer Treat Res. 1996;82:359–74.
18. Llueca A, Escrig J. MUAPOS working group (Multidisciplinary Unit of Abdominal Pelvic Oncology Surgery). Prognostic value of peritoneal cancer index in primary advanced ovarian cancer. Eur J Surg Oncol. 2018;44(1):163–9.
19. Lampe B, Kroll N, Piso P, Forner DM, Mallmann P. Prognostic significance of Sugarbaker's peritoneal cancer index for the operability of ovarian carcinoma. Int J Gynecol Cancer. 2015;25(1):135–44.
20. Colombo N, Guthrie D, Chiari S, Parmar M, Qian W, Swart AM, et al. International collaborative ovarian neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. J Natl Cancer Inst. 2003;95(2):125–32.
21. Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database Syst Rev. 2009;3(3):CD004706.
22. Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, De Placido S, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2014;15(4):396–405.
23. Wu YS, Shui L, Shen D, Chen X. Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. Oncotarget. 2017;8(6):10703–13. https://doi.org/10.18632/oncotarget.12926.
24. Oza AM, Cook AD, Pfisterer J, et al. ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015;16:928–36.
25. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378:230–40. https://doi.org/10.1056/NEJMoa1708618.
26. Di Giorgio A, De Iaco P, De Simone M, Garofalo A, Scambia G, Pinna AD, et al. Cytoreduction (Peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer: retrospective Italian multicenter observational study of 511 cases. Ann Surg Oncol. 2017;24(4):914–22.
27. Kim JH, Chun SY, Lee DE, Woo YH, Chang SJ, Park SY, Chang YJ, Lim MC. Cost-effectiveness of hyperthermic intraperitoneal chemotherapy following interval cytoreductive surgery for stage III-IV ovarian cancer from a randomized controlled phase III trial in Korea (KOV-HIPEC-01). Gynecol Oncol. 2023;170:19–24.
28. Lim MC, Chang SJ, Park B, Yoo HJ, Yoo CW, Nam BH, Park SY, HIPEC for Ovarian Cancer Collaborators. Survival after hyperthermic intraperitoneal chemotherapy and primary or interval cytoreductive surgery in ovarian cancer: a randomized clinical trial. JAMA Surg. 2022;157(5):374–83. https://doi.org/10.1001/jamasurg.2022.0143.

29. NCCN Guidelines Version 1.2023 Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
30. Suidan RS, Ramirez PT, Sarasohn DM, Teitcher JB, Mironov S, Iyer RB, et al. A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer. Gynecol Oncol. 2014;134(3):455–61.
31. Fagotti A, Ferrandina G, Fanfani F, Ercoli A, Lorusso D, Rossi M, Scambia G. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. Ann Surg Oncol. 2006;13(8):1156–61.
32. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of clinical oncology clinical practice guideline. J Clin Oncol. 2016;34(28):3460–73.
33. Food and Drug Administration. Highlights of Prescribing Information: AVASTIN® (bevacizumab). 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf.
34. Bogani G, Matteucci L, Tamberi S, Ditto A, Sabatucci I, Murgia F, et al. RECIST 1.1 criteria predict recurrence-free survival in advanced ovarian cancer submitted to neoadjuvant chemotherapy. Eur J Obstet Gynecol Reprod Biol. 2019;237:93–9.
35. Ditzel HM, Strickland KC, Meserve EE, et al. Assessment of a chemotherapy response score (CRS) system for Tubo-ovarian high-grade serous carcinoma (HGSC). Int J Gynecol Pathol. 2019;38(3):230–40.
36. Bohm S, Faruqi A, Said I, Lockley M, Brockbank E, Jeyarajah A, et al. Chemotherapy response score: development and validation of a system to quantify histopathologic response to neoadjuvant chemotherapy in tubo-ovarian high-grade serous carcinoma. J Clin Oncol. 2015;33(22):2457–63.
37. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.
38. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249–57.
39. Onda T, Satoh T, Saito T, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan clinical oncology group study JCOG0602. Eur J Cancer. 2016;64:22–31.
40. Onda T, Satoh T, Ogawa G, et al. Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial. Eur J Cancer. 2020;130:114–25.
41. Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. Eur J Cancer. 2016;59:22–33.
42. Vergote I, Coens C, Nankivell M, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials [published correction appears in Lancet Oncol. 2019 Jan;20(1):e10]. Lancet Oncol. 2018;19(12):1680–7.
43. Fagotti A, Gueli Alletti S, Corrado G, Cola E, Vizza E, Vieira M, et al. The INTERNATIONAL MISSION study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy. Int J Gynecol Cancer. 2019;29(1):5–9.
44. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495–505.
45. Mathews CMK, Colombo N, Scambia G, et al. Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): efficacy by surgical and tumor status in the phase III SOLO1 trial. J Clin Oncol. 2019;37(suppl; abstr 5541).
46. González-Martín A, Pothuri B, Vergote I, et al. PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381:2391–402.
47. Ray-Coquard I, Pautier P, Pignata S, et al. PAOLA-1 Investigators. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381:2416–28.
48. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403–15.
49. Konstantinopoulos PA, Lheureux S, Moore KN. PARP inhibitors for ovarian cancer: current indications, future combinations, and novel assets in development to target DNA damage repair. Am Soc Clin Oncol Educ Book. 2020;40:1–16.
50. Chelariu-Raicu A, Zibetti Dal Molin G, Coleman RL. The new world of poly-(ADP)-ribose polymerase inhibitors (PARPi) used in the treatment of gynecological cancers. Int J Gynecol Cancer. 2020;30(10):1608–18.

3 Low-Grade Serous Ovarian Carcinoma

Anastasios Tranoulis

Introduction

Low-grade serous carcinoma of tubo-ovarian or peritoneal origin (LGSC) represents a rare subtype of epithelial ovarian cancer (EOC), accounting for approximately 2% of all EOC and 5% of serous EOC [1]. LGSCs are a distinct entity from a clinical, biological and molecular standpoint [2]. They usually arise from serous borderline ovarian tumours (SBOT) or as a de novo malignancy from the ovary or peritoneum [2, 3]. Compared to HGSCs, women with LGSCs are usually diagnosed at younger age and are more likely to be pre-menopausal; thus, indicating a plausible hormonal role in the pathogenesis [2–5].

The diagnosis and pre-operative work-up of women with LGSC are similar to those with HGSC and should include the CA125 assay, computed tomography (CT) of chest, abdomen and pelvis to ascertain the dissemination of the disease. Magnetic resonance imaging (MRI) is a useful adjunct to further characterizing pelvic masses, whilst the 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has a limited role in the pre-operative diagnostic process [2, 6].

Surgery represents the cornerstone of treatment amongst women with LGSC, as this subtype of EOC is characterized by marked chemoresistance [2, 6]. For advanced-stage LGSC, primary cytoreductive surgery (CRS) is the treatment of choice, and an attempt of primary maximal cytoreduction is required, whilst the role of neoadjuvant chemotherapy is rather controversial [2, 6]. Despite the high rate of chemoresistance, adjuvant chemotherapy is usually administered. LGSCs usually express oestrogen (ER) and/or progesterone receptors (PR); therefore, hormonal therapy (HT) represents one of the maintenance treatment options [2, 6]. Secondary cytoreductive surgery (sCRS), chemotherapy or HT are the treatment options in the recurrent setting [2, 6]. Finally MEK and CDK inhibitors are emerging molecular targeted treatment modalities, especially amongst women with recurrent LGSC [2, 6].

Case: 1 Low Grade Serous Ovarian Cancer Advanced Stage

Age, Parity	74 years nulliparous
Presenting complaints	Breathlessness, abdominal distension x 7 months

A. Tranoulis (✉)
Department of Gynaecological Oncology, The Pan-Birmingham Gynaecological Cancer Centre, Birmingham City Hospital, Birmingham, UK
e-mail: Anastasios.tranoulis1@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_3

Co morbidities	Chronic smoker with bronchiectasis, interstitial lung disease, BMI = 48, Hypo proteinemia (serum albumin 28 g/L) ECOG = 2
CECT chest+ abdomen+ pelvis	Pleural effusion, ascites, omental cake + Peritoneal nodules+ Left ovarian mass 7 × 8 cm, uterus normal
Pleural fluid cytology	Positive for malignancy
Image guided biopsy	Low grade serous carcinoma CK 7+, CK20-ve, PAX8 + ve, p53 wild type, ER-ve
Tumor markers	CA125: 520 U/mL

Q: Role of Neoadjuvant Chemotherapy in Advanced Cases of Low Grade Serous Cancer?

NACT followed by delayed cytoreductive surgery (dCRS) has a controversial role in advanced-stage LGSC, as the reported response rate to chemotherapy in this setting is rather low [7, 8]. Schmeler et al. previously reported that after a median of 6 cycles of platinum-based NACT, the complete response and stable disease rate was 4% and 88%, respectively [7]. Similarly, Cobb et al. showed that after a median of 5 cycles of platinum-based NACT, the partial response, stable disease and progressive-disease rate was 11%, 83% and 6%, respectively [8]. Interestingly, 81% of the women underwent dCRS and complete cytoreduction (CC-0) was achieved in only 38% [8].

Primary cytoreductive surgery (pCRS) represents the cornerstone of treatment and a maximal effort for CC-0 resection should be attempted when possible [2, 6]. Nonetheless, patient selection is a key factor in recommending the optimal initial management approach. When choosing between pCRS and NACT several parameters should be taking into account: (1) Age and frailty; (2) Co-morbidities; (3) Performance status; (4) Nutritional status; (5) Stage and resectability of the disease (e.g. extensive small bowel disease, stage IV); (6) sufficient surgical and intensive care unit (ITU) resources.

Q: How Many Cycles of Neoadjuvant Chemotherapy Should Be Given 4 Versus 6 cycles? How to Assess Response to NACT?

The standard management of advanced-stage EOC in the NACT setting consists of 3–4 cycles of NACT followed by dCRS [9, 10]. Response to NACT should be evaluated by imaging (CT scan) and serological CA-125 values in between cycles. The radiological response classifies the findings into 3 categories: (1) Complete or partial response; (2) Stable disease; (3) Progressive disease. Complete cytoreduction is the single most important prognostic factor for overall survival [9, 10]. CHORUS [9] and EORTC [10] trials demonstrated the importance of complete cytoreduction for dCRS after 3 or 4 cycles of NACT. In case of persistent disease, the evidence concerning the role of CRS after +5 cycles of NACT is limited. A recent multicentre study demonstrated favourable oncological outcomes of "very delayed" CRS (after 5 or 6 cycles of NACT) if CC-0 resection can be achieved [11]. This evidence is in line with smaller observational studies [12].

Q: Discuss Preoperative Optimisation in this Patient?

This was a case of a 74-year old patient with morbid obesity (BMI = 48) and significant past medical history, including interstitial lung disease. At diagnosis, her WHO performance status was 2, whist the low albumin levels indicated an impaired nutritional status. Interestingly, low albumin levels have been found to be a survival prognosticator amongst women with advanced-stage EOC [13]. Finally, the pleural effusion cytology was positive for malignancy, therefore, this was a FIGO stage IVA disease. The extensive pleural effusions are usually an indicator of significant pleural disease, which cannot be resected in the pCRS setting. The combination of the aforementioned factors was taken into account by the relevant multidisciplinary team (MDT) and a consensus for NACT followed by dCRS was reached. In such cases it is of utmost importance a definite histological diag-

nosis to be made prior to initiating treatment. Indeed, in this case the image-guided biopsy confirmed the diagnosis of a LGSC.

The patient demonstrated partial response after 4 cycles of NACT. Owing to the sub-optimal radiological response in addition to the low performance and nutritional status and the severe co-morbidities a decision was made for completion of NACT. Following 6 cycles of NACT, the patient showed good response with complete resolution of the ascites and pleural effusions, in addition to the improvement of her performance and nutritional status. In light of this response, a decision was made for "very delayed" CRS.

Women undergoing major CRS for advanced-stage EOC are predisposed to a decrease in functional capacity as a response to surgical stress, which can delay post-operative recovery. In such cases, multimodal pre-habilitation programmes are important for the pre-operative optimisation with a view to improve functional capacity and enhance post-operative recovery. Multimodal pre-habilitation may include exercise, nutritional counselling, psychological support, and optimisation of underlying medical conditions (e.g. chest function in this case), as well as cessation of unfavourable health behaviours such as smoking and drinking [14]. Anaesthetic pre-assessment is also important in such cases in order to secure optimal peri-operative anaesthetic support and access to intensive care unit facilities [14].

Q: What Is the Route for Surgery? Is There any Role of Laparoscopy in LGSOC?

Median xyphopubic laparotomy remains the standard surgical approach in case of advanced-stage EOC in pCRS and dCRS setting. With the wide-spread use of NACT in advanced-stage EOC, the use of laparoscopic dCRS has recently gained popularity. Although in the case of diffuse intra-abdominal disease the use of the laparoscopic approach for complete dCRS is not indicated, there may be a role for laparoscopic dCRS for low-volume disease. MISSION and CILOVE trials demonstrated encouraging results of minimally invasive dCRS in advanced-stage EOC [15, 16]. The ongoing LANCE trial is perfectly designed to further delineate the role of minimal access surgery in advanced-stage EOC after NACT [17].

Case 1

Due to extensive disease and poor pre operative optimization, decision was taken to start neo adjuvant chemotherapy in MDT.

After 4 cycles there was partial response: pleural effusion had resolved, ascites reduced, PS-2, Serum albumin: 32 g/L. Chemotherapy continued for two more cycles.

After 6 cycles: complete resolution of ascites. CECT: omental cake, left ovarian mass 5 cm;

Serum albumin: 35 g/L. PS-1. Patient planned for surgery.

Surgery: Total hysterectomy, bilateral salpingo-oophorectomy, supracolic omentectomy (CC-0).

Case 2 Low Grade Serous Ovarian Cancer with Liver Metastasis

Age, parity	49 years, P2 + 0previous 2 cesareans
Presenting complaints	Abdominal distension × 5 months
Co morbidities	History of ileocolic resection for ruptured appendix, depression ECOG = 1
CECT chest+ abdomen+ pelvis	Diaphragm deposits, omental cake +, mild ascites Peritoneal nodules+, multiple bowel deposits, superficial liver metastasis segment VI Left ovarian mass 7 × 8 cm, uterus normal
Tumor markers	CA125: 395 U/mL, CEA: 3 ng/mL
Image guided biopsy	Low grade serous carcinoma CK 7+, CK20-ve, PAX8 + ve, p53 wild type, ER + ve

Q: What Are the Points To Be Considered Which Will Help Us Decide Management? What Are the Management Options?

The parameters that should be considered when planning upfront treatment include: (1) Age and frailty; (2) Co-morbidities; (3) Performance status; (4) Nutritional status; (5) Stage and resectability of the disease (e.g. stage IVA, unresectable stage IIIC or IVB); (6) histology (HGSC, LGSC, endometrioid, mucinous, clear cell, carcinosarcoma); (7) Insufficient surgical and ITU resources.

Q: Discuss the Role of Primary Debulking Surgery Versus Delayed Debulking Surgery in Low Grade Serous Ovarian Cancer?

Although 2 randomised clinical trials failed to demonstrate the superiority of pCRS over NACT followed by DDS, this evidence mainly applies to HGSC [9, 10]. In light of the poor response of LGSC to NACT, PDS should be considered as the treatment of choice [2, 6]. A maximal effort for CC-0 cytoreduction should be attempted. However, the aforementioned parameters should also be taken into consideration when planning the upfront treatment management of women with LGSC. As demonstrated in GOG 182 study, women with CC-0 pCRS had significantly better overall (OS) and progression-free survival (PFS) vis-a-vis their counterparts with CC-1 [18]. Therefore all women with suspected or confirmed LGSC should be referred to a specialized tertiary gynaecological oncology centre and assessed by the relevant MDT for feasibility of pCRS. In such cases, it is of utmost importance to obtain a definite histological diagnosis prior to initiating treatment.

Q: What Are the Clinical, Histological and Molecular Distinguishing Features of Low-Grade Serous Cancer from High-Grade Epithelial Ovarian Cancer?

LGSC represents a distinct entity from a clinical, histological and molecular standpoint [2, 6]. Compared to HGSC, women with LGSC are often diagnosed at younger age and are more likely to be pre-menopausal [2, 6]. The latter indicates a plausible hormonal role in the pathogenesis [2, 6]. Furthermore, LGSC is characterized by marked chemoresistance but better prognosis compared to HGSC [2, 6].

LGSC is characterised by a monotonous population of cuboidal, low columnar, and sometimes flattened cells with an amphophilic or lightly eosinophilic cytoplasm. LGSCsusually demonstrate destructive invasion, mild to moderate cytologic atypia, and relatively low proliferative activity (i.e., a mitotic index <12 mitoses/10 HPF). Moreover, LGSC does not exhibit nuclear pleomorphism and usually lacks tumour cell necrosis, factors often present in HGSC [2, 6, 19].

In terms of its immunophenotype, LGSC is usually positive for *WT-1*, *PAX8* and *CK7*, and negative for *CK20* staining. The *p53* expression pattern in LGSC is usually compatible with wild-type p53 (*wt-p53*), although it can be aberrant in a small proportion of cases. *p16* expression is usually heterogeneous, whilst *Ki-67* index is usually <10%, although a higher index can be seen in a few occasions. *HER2/neu* is positive in up to 28% of the cases [19, 20]. Finally, LGSCs are positive for oestrogen receptors (ER) in the vast majority of cases, and progesterone receptors (PR) in some cases [21–25].

LGSCs are usually develop form SBOTs, and only occasionally as a de novo malignancy from the ovary or peritoneum [2, 6]. Unlike their

HGSC counterparts, LGSCs are rarely associated with *BRCA* and *p53* mutations. LGSCs are usually associated with activating mutations of genes enrolled in the mitogen activated protein kinase (*MAPK*), including *KRAS*, *BRAF*, *ERBB2*, and *NRAS*, in addition to other driver mutations (*PIK3CA*, *FFAR1*, *USP9X*, *EIF1AX*) enrolled in the *AKT-mTOR* pathway, which is also a moderator of *MAPK* pathway [2, 6].

Q: What Is the Pre-operative Preparation Required in this Case?

In light of the radiological and histological findings, a referral to the gynaecological oncology and hepatobiliary MDT is required to evaluate the respectability of the disease. An appropriate assessment and consultation is required by both the gynaecological oncology and hepatobiliary team, as this patient is likely to require a joined ('buddy') procedure. Furthermore, a pre-operative anaesthetic review is warranted in order to secure optimal peri-operative anaesthetic support and access to ITU facilities. Finally, pre-operative optimisation with multimodal pre-habilitation plays an important role in improving functional capacity and enhancing post-operative recovery.

Case 2

Surgery: Extra-peritoneal total hysterectomy + bilateral salpingo-oophorectomy + supra-colic omentectomy+ total peritonectomy+ cholecystectomy+ right and left diaphragmatic stripping+ Segment VI partial liver resection+ splenectomy+ Morisson's pouch peritonectomy+ total colectomy+ terminal ileostomy (CC-0).

Final HPE: Low-grade serous ovarian cancer ER + ve, p53 wild type. FIGO stage IVB.

Patient was discharged on Day 8.

Q: What Is the Role of Adjuvant Chemotherapy?

LGSC represents an indolent malignancy, which is characterised by a marked chemoresistance. The reported response rates of LGSCs to adjuvant chemotherapy ranged between 4% and 25% [2, 4–6]. In the ad-hoc analysis of AGO-OVAR phase III trial, 145 women with LGSC who underwent pCRS + adjuvant chemotherapy were identified. 24.1% had CC > 1 and were evaluable for response to adjuvant chemotherapy. An objective response was observed in 23.1%, which was significantly lower vis-a-vis 90.1% response rate in their HGSC counterparts with CC > 1 [26]. In the absence of robust evidence arising from randomised clinical trials, some clinicians manage LGSC similarly to HGSC, whilst others have completely abandoned adjuvant chemotherapy in favour of HT.

Q: Is There any Role of Maintenance Therapy?

Approximately 95% of women with LGSC will have positive ER tumoral expression, whilst more than half of them will demonstrate +PR expression [2, 6]. Therefore, HT administered as a sole treatment after CRS or as maintenance treatment after CRS and adjuvant chemotherapy represents an important treatment modality amongst women with LGSC.

A recent retrospective study from the MD Anderson Cancer Centre group enrolling 203 women with stage II–IV LGSC, who received maintenance HT (letrozole, anastrozole, tamoxifen) following pC RS + adjuvant chemotherapy or NACT+ dCRS+ adjuvant chemotherapy demonstrated a better PFS in HT compared to surveillance group (64.9 vs 26.4 months); notwithstanding, no significant difference in OS was observed between groups (102.7 v 115.7 months) [27]. In another observational study, HT was administered instead of chemo-

therapy after CRS amongst women with LGSC. The reported 3-year PFS and OS were 79% and 92.6%, respectively [24]. It is recommended that HT should be continued until disease progression or significant toxicity occurs. During the treatment course, the bone density and lipid levels should be regularly monitored, as hyperlipidaemia and osteoporosis are common side-effects related to HT [2, 6].

Q: What Is the Role of BRCA/HRD Testing in LGSOC?

LGSCs are rarely associated with chromosomal instability caused by BRCA mutations. Occasionally, BRCA mutations can be found, especially in the Ashkenazi jewish populations. Nonetheless, genetic testing including gBRCA, tBRCA, and HRD testing is currently recommended in all women with new diagnosis of non-mucinous, and non-borderline tubo-ovarian or primary peritoneal carcinoma [2, 6].

Case 3: Recurrent Low Grade Serous Ovarian Cancer

Age, parity	37 years, P1 + 0
Presenting complaints	Pain abdomen × 5 months
Co morbidities	Known case of serous borderline ovarian tumor with invasive omental implants (stage III c) History of primary debulking surgery(CC-0) (2014): Extra-peritoneal hysterectomy + bilateral salpingo-oophorectomy + supra-colic omentectomy
CECT chest+ abdomen+ pelvis	8 × 7 cm mass at pylorus of stomach with rectosigmoid thickening
Tumor markers	CA125: 140 U/mL, CEA: 7 ng/mL
Image guided biopsy	Low grade serous carcinoma CK 7+, CK20-ve, PAX8 + ve, p53 wild type, ER PR + ve

Q: What Are the Treatment Options for Recurrent LGSC?

More than 70% of the women with FIGO stage III-IV will experience a disease relapse [2, 6]. A number of treatment options are available in this setting, including secondary cytoreductive surgery (sCRS), chemotherapy, HT and targeted agents [2, 6]. Similarly to the primary setting, the response rate of recurrent LGSC to chemotherapy is lower than 5%; notwithstanding, the stable disease rate may be as high as 60% [28, 29]. In light of the aforementioned chemoresistance, and the excellent outcomes of CRS (especially when CC-0 resection can be achieved), sCRS with maximal surgical effort is recommended for highly selected patients, who are deemed eligible for CC-0 resection, as failure to achieve complete or at least optimal cytoreduction is a poor prognosticator. In a retrospective study by the MD Anderson team, 41 women with recurrent LGSC underwent sCRS and the reported CC-0 rate was 78% [30]. The PFS in the CC-0 group was 60.3 months vis-a-vis 10.7 months in the group with gross residual disease. The OS in the CC-0 group trended towards statistical significance, yet, when assessing the OS from the tome of sCRS, this was significantly longer in the CC-0 group. Finally, HT has a pivotal role in recurrent LGSC. The reported rates to anti-oestrogen therapies range between 9% and 14%, whilst the reported stable disease rates are as high as 60% [31, 32].

Q: What Is the Significance of Invasive Implants with Serous Borderline Ovarian Tumours? What Is the Prognosis in Comparison to Low Grade Serous Cancers?

Approximately 30% to 50% of women with SBOT develop extra-ovarian pelvic and/or intra-abdominal spread in the form of tumour implants

[33]. The histologic classification of these implants into invasive and noninvasive types is currently the most important prognosticator factor in women with high-stage disease [33]. Because the presence of extra-ovarian invasive implants is linked with a similar OS to that of LGSC, the designation LGSC is recommended [33]. The presence of invasive implants should be confirmed by at least two pathologists in order to establish the diagnosis of LGSC [33]. The key criterion for diagnosing invasive implants in SBOT is low-power destructive tissue invasion, which is associated with varying degrees of stromal response [33].

Case 3

Partial gastrectomy with Roux-en-Y, Hartmann's procedure, pelvic peritonectomy and removal of bulky pelvic and para-aortic lymph nodes (CC-0).

Post-operative recovery: uneventful.

Histology: Low grade serous cancer ER,PR + ve.

Q: What Is the Further Management in this Patient?

The residual disease is seemingly the more significant prognosticator amongst women undergoing sCRS for recurrent LGSC. In this case scenario, a sCRS was performed with maximal surgical effort and increased surgical complexity, which resulted in a CC-0 resection. As mentioned above, LGSC are relatively chemoresistant in both primary and recurrent setting, and the reported response rates of recurrent LGSC to chemotherapy are rather disappointing (<5%) [2, 4–6, 28, 29]. In the absence of robust evidence arising from randomised clinical trials, there is an uncertainty as to whether adjuvant chemotherapy improves survival, especially when a complete CRS was achieved. To this end, many clinicians manage recurrent LGSC in the same context as their HGSC counterparts or have abandoned the use of adjuvant chemotherapy in favour of HT. Finally, the role of anti-angiogenic agents such as bevacizumab and other molecularly targeted agents including MEK, PI3K and cyclin-dependent kinase (CDK) 4/6 inhibitors either as a single modality treatment or in combination with chemotherapy and/or HT is currently under evaluation [2, 6]. The molecular targeted agents tested in LGSC are depicted in Table 3.1.

Table 3.1 Targeted agents used in low-grade serous carcinoma of ovary or peritoneum

Antiangiogenic agent	Bevacizumab
MEK inhibitors	Trametinib Selumetinib Pimasertib Binimetinib
PI3K inhibitor	Voxtalisib
CDK 4/6 inhibitors	Ribociclib Abemaciclib

Case 4: Fertility Preservation in Low Grade Serous Ovarian Cancer

Age, parity	25 years, unmarried
Presenting complaints	Lump abdomen, abdominal distension ×1 year Examination: 18 weeks size mass
Co morbidities	Hypothyroidism
CECT chest+ abdomen+ pelvis	13 × 8 cm solid cystic mass in the left ovary, 15 × 10 cm mass arising from the right ovary, uterus normal size, omental thickening +, no retroperitoneal nodes
Tumor markers	CA125: 340 U/mL, CEA: 4 ng/mL, AFP: 2 ng/mL, LDH: 140 U/L, BHCG: 2mIU/mL

Q: What Is the Further Management in this Case? Since both Ovaries Are Involved What Are the Fertility Preservation Options for the Patient?

According to ESMO and ESGO guidelines for the fertility preservation in EOC, a conservative approach is limited to FIGO stage IA grade 1 or 2, and IC EOC with unilateral involvement, in the case of serous, endometrioid, mucinous, or mixed

type histology [34]. In this case, both ovaries appear to be involved, whist there is high suspicion for omental involvement. Therefore, ovarian preservation cannot be recommended. Moreover, ovarian tissue cryopreservation or oocyte cryopreservation after controlled ovarian hyperstimulation (COH) is also not recommended in case of suspected ovarian cancer [34]. The preservation of the uterus does not appear to increase the risk of recurrence; hence, the only fertility sparing option in this case, is the preservation of the uterus and use of donor egg to achieve future pregnancy, if the latter is strongly desired after surgery. Nonetheless, in light of the high-risk of ovarian cancer a thorough consultation concerning the pros and cons of fertility sparing on oncological outcomes is warranted.

Case 4

After extensive counselling the patient underwent staging laparotomy, bilateral salpingo-oophorectomy, supra-colic omentectomy+ peritoneal biopsies and removal of implants from uterine surface + removal of left external and internal iliac enlarged nodes.

Histology: Low grade serous carcinoma bilateral ovaries, peritoneal biopsies and omentum show microscopic deposits. FIGO stage IIIA2, peritoneal cytology negative.

Q: What Is the Optimal Resection for Low-Grade Serous Carcinoma of Ovary or Peritoneum?

Residual disease status after primary CRS with maximal surgical effort is seemingly the strongest prognosticator associated with prolonged survival amongst women with LGSC. GOG-182 trial demonstrated that women with CC > 1 after primary CRS for LGSC had significantly higher recurrence rates (90.8%) compared to women with CC-0 (74.5%) [18]. Furthermore, the OS amongst women with CC > 1 resection was significantly shorter compared to those with no macroscopic residual disease (14.7 months versus 96.9 months) [18]. Similar findings were reported in the AGO-OVAR phase III trial [26]. The 5-year OS amongst women who underwent CRS with CC-0 was 85% compared to 32% in women with CC-1 or CC-2 resection [26].

Q: What Are the Adjuvant Treatment Options?

In this case, the patient underwent a primary CRS with maximal cytoreductive effort, which resulted in a CC-0 resection. As stated above, the residual disease after CRS in the strongest predictor of survival. As LGSC are characterised by poor response rates to chemotherapy and in view of the CC-0 resection, the patient can be spared from adjuvant chemotherapy. However, a thorough consultation is required by the medical oncology team concerning the pros and cons of adjuvant chemotherapy. An analysis of tumoral ER and PR status is warranted. In case of +ER and/or + PR expression and in the absence of any contraindications, maintenance anti-oestrogen HT can be offered. A regular monitoring of bone density and lipid levels is also required.

Q. What is the prognosis?

LGSC has a less aggressive behaviour and better prognosis compared to HGSC. An analysis of the SEER's database demonstrated that the mean OS was 99 months for LGCS vis-a-vis 57 months in HGSC [35]. Similarly, Okaye et al., reported that the 5-year OS in women with LGSC (62.3%) was significantly longer than those with HGSC (43.9%); notwithstanding; this advantage was diminished over time and the 10-year OS was not significantly different between the two groups [36].

Generally, women with FIGO stage I disease have excellent prognosis following comprehensive staging procedure. Fertility sparing management, with ovarian preservation can be offered in women with FIGO stage IA-IC LGSC wishing to maintain their fertility following thorough consul-

tation on the fertility and oncological outcomes. For FIGO stage IA and IB observation alone is a safe option, whilst for stage IC chemotherapy and/or HT can be offered [34].

For women with stages II-IV LGSC the prognosis is better compared to high-stage HGSC. As mentioned above, surgery represents the cornerstone of treatment and residual disease is the main prognosticator. The AGO-OVAR phase III trial showed that the 5-year OS amongst women who underwent CRS with CC-0 was significantly better compared to those with CC-1 or CC-2 (85% versus 32%) [26]. Therefore, maximal effort cytoreduction should be attempted followed by chemotherapy and/or HT. The presence of +ER/+PR represents an important prognostic factor. High tumoral expression is seemingly an independent prognostic factor in advanced-LGSC; whist low PR expression appears to be linked with a more aggressive clinical course [37]. The use of bevacizumab [38, 39] and the emerging molecular targeted agents- especially MEK inhibitors [2, 6] - have showed promising results in improving oncological outcomes in advanced and recurrent LGSC, however, their role needs to be evaluated further by future clinical trials.

Key Points

- LGSOC, a rare ovarian cancer subtype, may arise de novo or following diagnosis of serous borderline tumour.
- The presence of SBOT with extra-ovarian invasive implants is associated with a similar OS to that of LGSC and the designation LGSC is recommended.
- Surgery represents the cornerstone of treatment amongst women with LGSC. Fertility-sparing surgery can be offred to highly selected patients, whilst for those with advanced-stage disease maximal surgical effort is required to achieve CC-0 resection.
- LGSC are characterised by marked chemoresistance and the role of chemotherapy in both neoadjuvant and adjuvant setting is debatable.
- HT administered as a sole treatment after CRS or as maintenance treatment after CRS and adjuvant chemotherapy is an important treatment modality amongst worm with LGSC.
- A number of treatment options are available in the recurrent setting, including sCRS, chemotherapy, HT, bevacizumab, and targeted agents.

References

1. Matsuo K, Machida H, Grubbs BH, Sood AK, Gershenson DM. Trends of low-grade serous ovarian carcinoma in the United States. J Gynecol Oncol. 2018 Jan;29(1):e15.
2. Slomovitz B, Gourley C, Carey MS, Malpica A, Shih IM, Huntsman D, Fader AN, et al. Low-grade serous ovarian cancer: state of the science. Gynecol Oncol. 2020;156(3):715–25.
3. Kurman RJ, Sih I. The dualistic model of ovarian carcinogenesis: revisited; revised; and expanded. Am J Pathol. 2016;186:733–47.
4. Schlumbrecht MP, Sun CC, Wong KN, Broaddus RR, Gershenson DM, Bodurka DC. Clinicodemographic factors influencing outcomes in patients with low-grade serous ovarian carcinoma. Cancer. 2011;117:3741–9.
5. Gershenson DM, Bodurka DC, Lu KH, Nathan LC, Milojevic L, Wong KK, Malpica A, Sun CC. Impact of age and primary disease site on outcome in women with low-grade serous carcinoma of the ovary or peritoneum: results of a large single-institution registry of a rare tumor. J Clin Oncol. 2015;33:2675–82.
6. Gadducci A, Cosio S. Therapeutic approach to low-grade serous ovarian carcinoma: state of art and perspectives of clinical research. Cancers (Basel). 2020;12(5):1336.
7. Schmeler KM, Sun CC, Bodurka DC, Deavers MT, Malpica A, Coleman RL, Ramirez PT, Gershenson DM. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol. 2008;108(3):510–4.
8. Cobb LP, Sun CC, Iyer R, Nick AM, Fleming ND, Westin SN, Sood AK, Wong KK, Silva EG, Gershenson DM. The role of neoadjuvant chemotherapy in the management of low-grade serous carcinoma of the ovary and peritoneum: further evidence of relative chemoresistance. Gynecol Oncol. 2020;158(3):653–8.
9. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, Luesley D, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249–57.

10. Vergote I, Coens C, Nankivell M, Kristensen GB, Parmar MKB, Ehlen T, Jayson GC, et al. EORTC; MRC CHORUS study investigators. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol. 2018;19(12):1680–7.
11. Plett H, Filippova OT, Garbi A, Kommoss S, Rosendahl M, Langstraat C, Phadnis S, et al. Role of delayed interval debulking for persistent residual disease after more than 5 cycles of chemotherapy for primary advanced ovarian cancer. An international multicenter study. Gynecol Oncol. 2020;159(2):434–41.
12. Phillips A, Sundar S, Singh K, Nevin J, Elattar A, Kehoe S, Balega J. Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer. Eur J Surg Oncol. 2018;44(6):760–5.
13. Dai D, Balega J, Sundar S, Kehoe S, Elattar A, Phillips A, Singh K. Serum albumin as a predictor of survival after interval debulking surgery for advanced ovarian cancer (AOC): a retrospective study. J Investig Surg. 2022;35(2):426–31.
14. Fotopoulou C, Planchamp F, Aytulu T, Chiva L, Cina A, Ergönül Ö, Fagotti A, et al. European Society of Gynaecological Oncology guidelines for the perioperative management of advanced ovarian cancer patients undergoing debulking surgery. Int J Gynecol Cancer. 2021;31(9):1199–206.
15. Fagotti A, Gueli Alletti S, Corrado G, Cola E, Vizza E, Vieira M, Andrade CE, et al. The INTERNATIONAL MISSION study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy. Int J Gynecol Cancer. 2019;29(1):5–9.
16. Pomel C, Akladios C, Lambaudie E, Rouzier R, Ferron G, Lecuru F, Classe JM, et al. Laparoscopic management of advanced epithelial ovarian cancer after neoadjuvant chemotherapy: a phase II prospective multicenter non-randomized trial (the CILOVE study). Int J Gynecol Cancer. 2021;31(12):1572–8.
17. Nitecki R, Rauh-Hain JA, Melamed A, Scambia G, Pareja R, Coleman RL, Ramirez PT, et al. Laparoscopic cytoreduction After Neoadjuvant ChEmotherapy (LANCE). Int J Gynecol Cancer. 2020;30(9):1450–4.
18. Fader AN, Java J, Ueda S, Bristow RE, Armstrong DK, Bookman MA, Gershenson DM. Gynecologic Oncology Group (GOG) survival in women with grade 1 serous ovarian carcinoma. Obstet Gynecol. 2013;122:225–32.
19. Malpica A, Deavers MT, Lu K, Bodurka DC, Atkinson EN, Gershenson DM, Silva EG. Grading ovarian serous carcinoma using a two tier system. Am J Surg Pathol. 2004;28:496–504.
20. O'Neill CJ, Deavers MT, Malpica A, Foster H, McCluggage WG. An immunohistochemical comparison between low-grade and high-grade ovarian serous carcinomas: significantly higher expression of p53, MIB1, BCL2, HER-2/neu, and C-KIT in high-grade neoplasms. Am J Surg Pathol. 2005;29(8):1034–41.
21. Wong KK, Lu KH, Malpica A, Bodurka DC, Shvartsman HS, Schmandt RE, Thornton AD, et al. Gershenson significantly greater expression of ER.; PR; and ECAD in advanced-stage low-grade ovarian serous carcinoma as revealed by immunohistochemical analysis. Int J Gynecol Pathol. 2007;26:404–9.
22. Escobar J, Klimowicz AC, Dean M, Chu P, Nation JG, Nelson GS, Ghatage P, Kalloger SE, Köbel M. Quantification of ER/PR expression in ovarian low-grade serous carcinoma. Gynecol Oncol. 2013;128:371–6.
23. Sieh W, Köbel M, Longacre TA, Bowtell DD, DeFazio A, Goodman MT, Høgdall E, et al. Hormone-receptor expression and ovarian cancer survival: an ovarian tumor tissue analysis consortium study. Lancet Oncol. 2013;14:853–62.
24. Fader AN, Bergstrom J, Jernigan A, Tanner EJ 3rd, Roche KL, Stone RL, Levinson KL, Ricci S, Wethington S, Wang TL, et al. Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced low-grade serous ovarian carcinoma: reducing overtreatment without compromising survival? Gynecol Oncol. 2017;147:85–91.
25. Llaurado FM, Dawson A, Kim H, Lam N, Russell H, Bruce M, Bittner M, Hoenisch J, Scott SA, Talhouk A, et al. Hormone receptor expression and outcomes in low-grade serous ovarian carcinoma. Gynecol Oncol. 2020;157:12–20.
26. Grabowski JP, Harter P, Heitz F, Pujade-Lauraine E, Reuss A, Kristensen G, Ray-Coquard I, Heitz J, Traut A, Pfisterer J, et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO study group metadatabase. Gynecol Oncol. 2016;140:457–62.
27. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. J Clin Oncol. 2017;35:1103–11.
28. Bristow RE, Gossett DR, Shook DR, Zahurak ML, Tomacruz RS, Armstrong DK, Montz FJ. Recurrent micropapillary serous ovarian carcinoma. Cancer. 2002;95:791–800.
29. Gershenson DM, Sun CC, Bodurka D, Coleman RL, Lu KH, Sood AK, Deavers M, Malpica AL, Kavanagh JJ. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol. 2009;114:48–52.
30. Crane EK, Sun CC, Ramirez PT, Schmeler KM, Malpica A, Gershenson DM. The role of secondary cytoreduction in low-grade serous ovarian cancer or peritoneal cancer. Gynecol Oncol. 2015;136:25–9.
31. Gershenson DM, Sun CC, Iyer RB, Malpica AL, Kavanagh JJ, Borurka DC, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol. 2012;125:661–6.
32. Tang M, O'Connell RL, Amant F, Beale P, McNally O, Sjoquist KM, Grant P, et al. PARAGON: a phase II study of anastrozole in patients with estrogen receptor-positive recurrent/metastatic low-grade ovar-

ian cancers and serous borderline ovarian tumors. Gynecol Oncol. 2019;154(3):531–8.
33. McKenney JK, Gilks CB, Kalloger S, Longacre TA. Classification of Extraovarian implants in patients with ovarian serous borderline tumors (tumors of low malignant potential) based on clinical outcome. Am J Surg Pathol. 2016;40(9):1155–64.
34. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, Morice P, et al. ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019;30:672–705.
35. Plaxe SC. Epidemiology of low-grade serous ovarian cancer. Am J Obstet Gynecol. 2008;198:459.e1–9.
36. Okoye E, Euscher ED, Malpica A. Ovarian low-grade serous carcinoma: a clinicopathologic study of 33 cases with primary surgery performed at a single institution. Am J Surg Pathol. 2016;40:627–35.
37. Gallo D, De Stefano I, Grazia Prisco M, Scambia G, Ferrandina G. Estrogen receptor beta in cancer: an attractive target for therapy. Curr Pharm Des. 2012;18:2734–57.
38. Rose PG, Mahdi H, Jernigan A, Yang B. Activity of bevacizumab in patients with low-grade serous ovarian carcinoma. Int J Gynecol Cancer. 2016;26:1048–52.
39. Dalton HJ, Fleming ND, Sun CC, Bhosale P, Schmeler KM, Gershenson DM. Activity of bevacizumab-containing regimens in recurrent low-grade serous ovarian or peritoneal cancer: a single institution experience. Gynecol Oncol. 2017;145:37–40.

4 Non-serous and Rare Histologies of Ovarian Cancer

Susan Addley and Andrew Phillips

Non-serous ovarian cancers represent a rarer subset of ovarian cancer – yet encompass a wide range of clinical entities, exhibiting a spectrum of biological aggressiveness. For the purpose of this chapter, we will further discuss squamous cell, clear cell, endometrioid and neuroendocrine tumours of primary ovarian origin – with mucinous, germ cell and sex-cord stromal sub-types being addressed in the content of later chapters.

Squamous cell carcinomas of ovary are rare – accounting for less than 1% of all ovarian cancer cases. Most often arising in the context of malignant transformation within a mature cystic teratoma – or dermoid – SCC of ovary has, however, also been identified in association with other precursor benign pathologies, including endometriosis; as well as having potential to arise directly from the ovarian surface epithelium proper [1].

Brenner tumours of ovary are distinct in their histopathological resemblance to tumours of urothelial origin. The majority, 95%, are benign – with malignant breach of the fibromatous stroma in the remaining 5% accounting for <1/100 ovarian cancer cases [2]. Malignant Brenner tumours (MBT) are typically solid/cystic – with no defining radiological features to aid easy pre-operative diagnosis (see Figs. 4.1 and 4.2).

Clear cell carcinoma of primary ovarian origin again represents a rare entity. Up to 70% of such cases develop in the setting of pelvic endometriosis; and typically appear as either a solid mass or suspected endometriotic cyst, but with solid component. Histopathologically, hobnail cells arranged in solid, glandular or papillary patterns are diagnostic. This sub-type is aggressive, with poor chemosensitivity (see Fig. 4.3).

Endometrioid ovarian cancers are less obscure – being the second most common epithelial ovarian cancer, representing 10–15% of cases. Like clear cell, this sub-type have a strong association with co-existing endometriosis, evident in some 42%. Such tumours are classically solid/cystic; and develop bilaterally in a third of cases (see Figs. 4.4 and 4.5). Histologically, endometrioid ovarian cancers exhibit adenofibromatous growth patterns with squamous metapla-

S. Addley · A. Phillips (✉)
Derby Gynaecological Cancer Centre, University Hospitals of Derby and Burton NHS Foundation Trust, Royal Derby Hospital, Derby, UK
e-mail: susan.addley@nhs.net; Andrew.phillips6@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_4

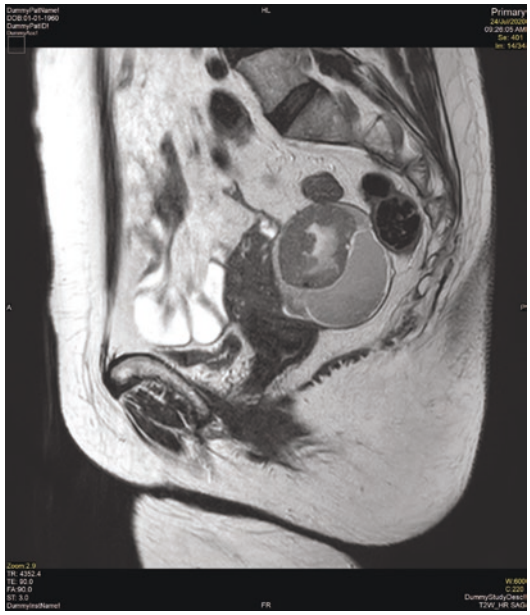


Fig. 4.1 Sagittal MRI image illustrating a malignant Brenner tumour (MBT)

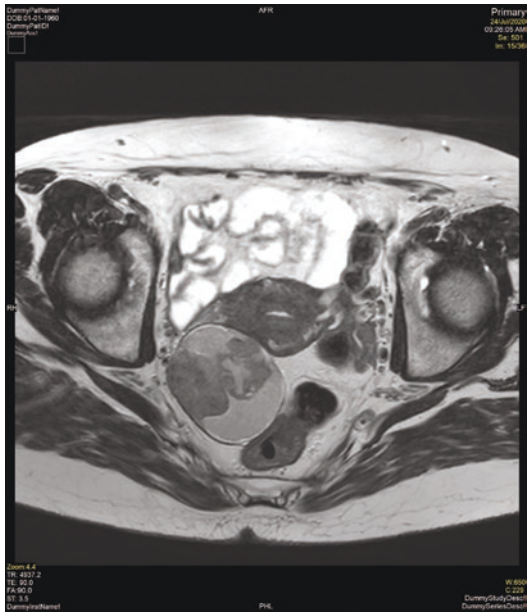


Fig. 4.2 Axial MRI image illustrating a malignant Brenner tumour (MBT)

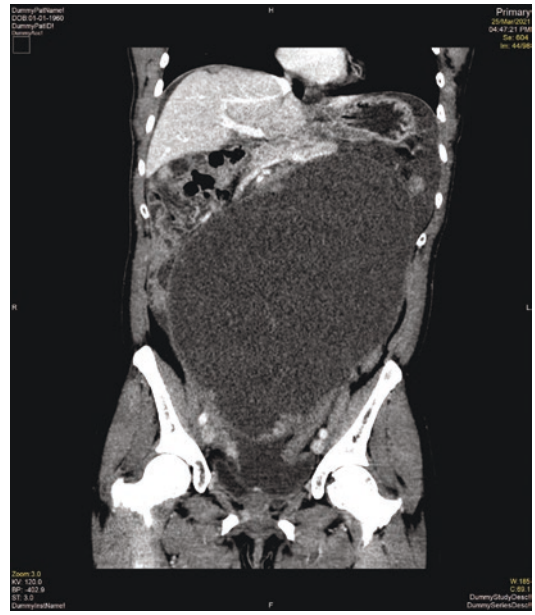


Fig. 4.3 Coronal CT image illustrating clear cell ovarian carcinoma with diaphragmatic metastasis

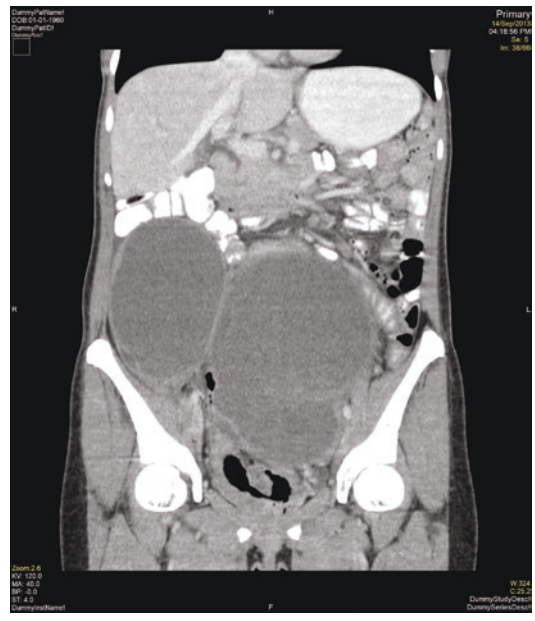


Fig. 4.4 Coronal CT image illustrating endometrioid ovarian carcinoma

sia; and are interestingly, in 15–20%, associated with concomitant carcinoma of the uterine endometrium proper. Traditionally considered to represent two distinct primaries, synchronous occurrence of these tumours is however increasingly believed to represent a metastatic process – evidenced by demonstrating clonal relations between lesions [3, 4].

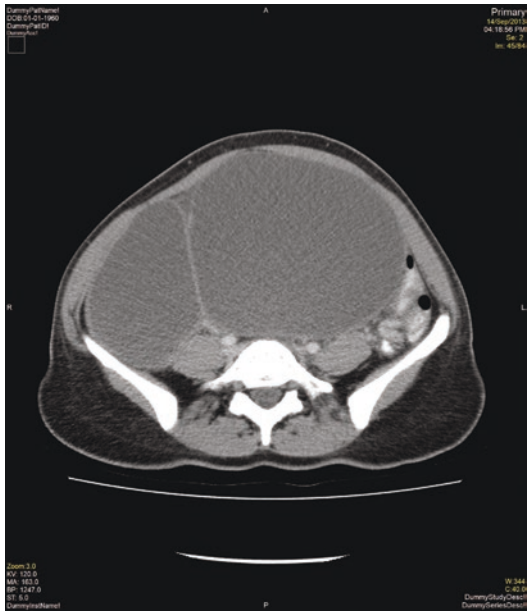


Fig. 4.5 Axial CT image illustrating endometrioid ovarian carcinoma

A 2020 revision of the WHO classification of neuroendocrine tumours of the ovary recognises two distinct entities – carcinoid and neuroendocrine carcinomas (NEC); representing low and high grade disease respectively. NEC are further sub-divided into small and large cell variants [5]. Primary ovarian carcinoid tumours tend to develop unilaterally; and – in contrast to gastrointestinal carcinoids – can manifest as carcinoid syndrome in the absence of liver metastasis, explained by direct passage of neuropeptides into the inferior vena cava via the alternative route of the ovarian vein [6]. NECs represent a more aggressive, and rare, neuro-endocrine tumour sub-type. Small cell variants encompass small cell carcinomas of the ovary of both pulmonary (SCCOP) and hypercalcaemic (SCCHC) type. Tumour secretion of neuropeptides again accounts for the associated hypercalcaemia, hypogylycaemia and SIADH which may develop. Large cell ovarian NEC essentially represents a category of undifferentiated non-small cell tumours; characterised by particularly aggressive behaviour and poor prognosis [7].

Case 1: Malignant Brenner Tumour

Age, PS	71 years, P0 + 1, ECOG −1, Body mass index (BMI) 36 kg/m^2
Clinical presentation	Under long-term follow-up with respiratory for chronic obstructive pulmonary disease (COPD) and previously noted indeterminate lung lesion. Progressive change of lesion noted on serial chest x-ray. Subsequent CT-PET suspicious for primary lung malignancy. Incidental finding of FDG-avid left adnexal mass. Bronchial washings confirmed mucinous adenocarcinoma of lung. Referred for gynae-oncological assessment of pelvic mass Abdominal examination: no ascites, Normal vulva, vagina, cervix. Bulky uterus. 6 cm left adnexal mass – mobile, no tethering
Co morbidities	COPD
MRI pelvis	6 cm complex left adnexal mass, concerning for malignancy. Nil extra-ovarian
Investigations	CA125: 223 U/mL, CEA: 28 ng/mL, CA19–9: 650 U/mL Serum albumin: 38 g/dL
Surgery (**joint lung/gynae MDT recommended management**)	1. Video-assisted thoracic surgery (VATS) - lung lobectomy and regional nodal clearance 2. Staging hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, peritoneal washings
Histology	Lung – adenocarcinoma with mucinous and papillary differentiation, involving surgical margins and regional nodes Pelvis – malignant Brenner tumour with squamous differentiation of left ovary, limited to focal involvement of ovarian capsule **Final diagnosis:** Primary T4N2M0adenocarcinoma of lung with synchronous primary FIGO stage1C2 malignant Brenner tumour of ovary
Joint lung/gynae MDT recommended further management	Adjuvant combined chemotherapy – Carboplatin and paclitaxel

Differential Diagnosis

1. Early primary lung cancer with synchronous early primary ovarian cancer
2. Advanced primary lung cancer with ovarian metastasis

Case 2: Clear Cell Carcinoma Ovary

Age, PS	54 years, nulliparous, WHO PS 1. BMI 30 kg/m^2
Clinical presentation	Presented to primary care with gradual onset of bloating and abdominal distension. Initially referred to the colorectal team. CT abdomen/pelvis identified a 20 cm ovarian mass – with moderate ascites, peritoneal and diaphragmatic nodularity. Onward referral to gynae-oncology Normal vulva and vagina. Cervix poorly visualised. No tense ascites. 20 cm pelvic mass – fixed, tethered to sigmoid
Co morbidities	Nil
Investigations	CA125: 320 U/mL CEA: 2 ng/mL CA19–9: 30 U/mL Serum albumin: 42 g/dL CT chest for completion staging: normal
Surgery (**joint lung/ gynae MDT recommended management**)	Primary debulking surgery **Intra-operative gynae-oncological findings** Large, adherent ovarian mass – with associated widespread peritoneal nodularity, omental cake, diaphragm and surface gallbladder disease. Enlarged para-aortic and coeliac axis nodes. Complete cytoreduction (R0) achieved
Histology	Clear cell carcinoma of ovarian origin, with metastatic involvement confirmed in all specimens. HRD-negative. **Final diagnosis** Primary FIGO stage3c clear cell carcinoma of ovary
Gynae MDT recommended further management	Adjuvant combined chemotherapy – Carboplatin and paclitaxel

Case 3: Endometrioid Ovarian Carcinoma

Age, PS	29 years, Nulliparous, ECOG −0, BMI 25 kg/m^2
Clinical presentation	Attended GP with new-onset, persistent abdominal distension. Background history of menorrhagia and dysmenorrhoea. Referral to gynae-oncology for assessment Normal vulva, vagina, cervix. No tense ascites. 10 cm pelvic mass– mobile, no tethering. Thickening of uterosacral ligaments, no nodularity in pouch of Douglas (POD)
Co morbidities	Nil
Imaging	US pelvis: 15 and 8 cm bilateral complex pelvic masses CT chest/abdomen/pelvis: Bilateral ovarian masses. Nil extra-ovarian
Investigations	CA125: 65 U/mL, CEA: 2.3 ng/mL, CA19–9: 30 U/mL HCG: <5, LDH: 220, AFP: 2 Serum albumin: 40 g/dL
Surgery (**joint lung/ gynae MDT recommended management**)	Discussion with patient 1. Staging hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, peritoneal washingsVersus 2. Potentially fertility-sparing conservative management (unilateral salpingo-oophorectomy/ovarian cystectomy) **Intra-operative** Unilateral oophorectomy and cystectomy requested by patient. 15 and 8 cm bilateral ovarian masses, with nil extra-ovarian. Unilateral oophorectomy and contra lateral cystectomy performed, with intra-operative rupture – expelling chronic haemorrhagic content
Histology	Bilateral endometriomata, with grade 1 endometrioid ovarian carcinoma arising within both cysts. Capsular penetration of left cyst wall Final diagnosis: Primary FIGO stage 1c (at least) endometrioid ovarian carcinoma

Gynae MDT recommended further management	Completion staging surgery (total hysterectomy, unilateral salpingo-oophorectomy, omental biopsy, peritoneal washings); followed by adjuvant combined chemotherapy – Carboplatin and paclitaxel

What Are Appropriate Investigations and Staging?

No additional diagnostic investigations are formally advised beyond NICE and BGCS-recommended tumour marker profile (CA125, CEA, CA19.9); pelvic ultrasound; and staging CT-chest/abdomen/pelvis to differentiate rare ovarian tumour types from more prevalent histopathologies. If, however, systematic questioning or clinical assessment identify symptoms or signs raising suspicion for carcinoid syndrome – 24 h urinary 5 hydroxyindoleacetic acid (HIAA) would support a diagnosis of neuroendocrine aetiology; and subsequent octreotide scanning be of diagnostic value.

As for all tubo-ovarian and peritoneal malignancies – ovarian SCC, MBT; clear cell; endometrioid; and NEC are assigned provisional radiological and subsequent surgical staging according to the FIGO (2014) staging system [8]. For a summary of correlation between current FIGO and TNM classification – as advocated by the Union for International Cancer Control – see Table 4.1.

Table 4.1 International Federation of Gynaecology and Obstetrics staging for cancers of the ovary, fallopian tube and peritoneum (2014)

FIGO stage	Pathological descriptors	TNM classification
I	Stage I: Tumor confined to ovaries or fallopian tube(s)	T1 – N0 – M0
IA	Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1a – N0 – M0
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1b – N0 – M0
IC IC1 IC2 IC3	Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following: IC1: Surgical spill IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in the ascites or peritoneal washings	T1c – N0 – M0 T1c1 – N0 – M0 T1c2 – N0 – M0 T1c3 – N0 – M0
II	Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	T2 – N0 – M0
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	T2a – N0 – M0
IIB	Extension to other pelvic intraperitoneal tissues	T2b – N0 – M0
III	Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T1–3 – N0–1 – M0
IIIA1 IIIA1(i) IIIA1(ii)	Positive retroperitoneal lymph nodes only (cytologically or histologically proven): IIIA1(i) metastasis up to 10 mm in greatest dimension IIIA1(ii) metastasis more than 10 mm in greatest dimension	T1–2 – N1 – M0
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a2 – N0–1 – M0
IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b – N0–1 – M0

(continued)

Table 4.1 (continued)

FIGO stage	Pathological descriptors	TNM classification
IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	T3c – N0–1 – M0
IV	Distant metastasis excluding peritoneal metastases	Any T, any N, M1
IVA	Pleural effusion with positive cytology	Any T, any N, M1
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	Any T, any N, M1

What Is the Primary Management of Early Stage Disease?

All women with suspected early stage ovarian cancer should be offered surgical staging – undertaken by a gynaecological-oncologist, who is a core member of a specialist multidisciplinary-team (MDT). Such surgery should include peritoneal washings/ascitic sampling (obtained prior to manipulation of the tumour), total hysterectomy with bilateral salpingo-oophorectomy, multiple peritoneal/diaphragmatic biopsies, omentectomy and bilateral pelvic/para-aortic lymph node assessment (up to the level of the renal veins) [9].

More often, however, in the context of rare ovarian tumours – given the not uncommon overlap of such with benign pre-cursors, such as dermoids and endometriosis – is to make an unanticipated *post-operative* diagnosis of malignancy following surgery for presumed benign disease. Such patients should be radiologically staged; and offered completion staging surgery – again, performed by a sub-specialist gynaecological-oncology surgeon. In histologically-proven MBT and NEC, the benefit of staging lymphadenectomy, however, remains debatable [2, 10].

As with all patients considering a fertility-sparing approach to early stage ovarian cancer – this warrants appropriate patient selection and adequate counselling. Patients with high grade endometrioid or clear cell ovarian carcinoma should be advised of a potentially higher risk of future recurrence with fertility-preservation – conferring a 10 year relapse-free survival of 70%; versus 90% in low grade counter-parts [11].

What Is the Primary Management of Advanced Stage Disease?

As final histology is often not known prior to primary debulking surgery (PDS) – the standard paradigm to offer upfront surgery if patient fit and complete cytoreduction achievable should be applied empirically to a clinical picture suggestive of 'advanced ovarian cancer'. RCTs have, however, confirmed survival benefit of such an approach in clear cell and endometrioid ovarian sub-types [12–14]. A greater paucity of data exists pertaining to PDS in SCCs, MBT and neuroendocrine carcinomas of ovarian origin – limited to retrospective SEER data [7] and case reports. If tumour histology is known pre-operatively – consideration should also be given to inherent tumour biology, as well as chemosensitivity, when debating PDS versus interval surgery. Patients must be counselled as to the limitation of evidence to guide such decision-making.

What Adjuvant Treatment Could Be Considered?

The evidence base to guide adjuvant therapy in the context of SCC of ovarian origin and MBT is limited. Retrospective SEER data, however, concluded radiotherapy as unlikely to be of benefit in ovarian squamous disease; whilst such tumour response appears to favour alkylating agent over platinum-based systemic therapy if extra-ovarian spread [15]. By contrast, MBT chemotherapy

response to combination Carboplatin/Paclitaxel demonstrates greater correlation with that exhibited by serous sub-type, making this the regime of choice [2].

International guidelines advise platinum-based chemotherapy as optional in patients with FIGO stage 1A to 1C1 clear cell ovarian carcinoma; but recommend if more advanced stage. The same guidance supports the safe omission of adjuvant treatment in low grade (1 and 2) endometrioid ovarian carcinoma limited to one ovary; but advise as optional for those with stage 1B through to stage 1C3 disease. For patients with more advanced low grade endometrioid pathology, or high grade of any stage, platinum-based chemotherapy is recommended as standard [16]. For both sub-types, the value of novel treatments is evidenced by the findings of both the GOG-0218 [17] and ICON 7 trials [18]– justifying additional Bevacizumab in those with advanced clear cell and endometrioid ovarian disease. PARP inhibitors were used with benefit in the context of endometrioid ovarian cancers in the SOLO1 and PRIMA trials, albeit in small numbers [19, 20].

Adjuvant therapy for neuroendocrine tumours should be agreed following specialist neuro-endocrine input; and is guided in part by Ki-67 status. Ki-67 < 30% indicates low grade pathology – in which additional treatment with somatostatin analogues may be considered. High grade NECs, characterised by Ki-67 > 30%, are poorly differentiated and aggressive tumours – warranting systemic chemotherapy with combination Etoposide/Cisplatin or Platinum-based chemotherapy for small and large cell ovarian respectively; with or without radiation [5].

How Would You Manage Recurrent Disease?

As for the primary management of rarer ovarian sub-types, approach to surgical management of recurrence is – inmost – derived from extrapolation of data pertaining to serous groups; with some, albeit limited, dedicated evidence also existing to support secondary cytoreduction in ovarian clear cell and endometrioid relapse. It is the author's opinion that further extrapolation of DESKTOP3, SOC1 and GOG-0213 findings to ovarian SCCs and MBT may not be unreasonable – but caution the importance of diligent adherence to stringent patient selection criteria as described in the literature [21–23]. Oncological management of recurrence – including additional lines of chemotherapy and PARP-inhibitor maintenance – is often again derived from serous data. Relapsed neuroendocrine tumours are particularly aggressive – hence individualized management, including careful evaluation of previous responses to treatment, is advised.

How Should These Women Be Best Followed-Up?

No clear consensus has been reached on the approach to long-term follow-up of gynaecological malignancies – with geographical and institutional variation in surveillance regimes for all cancer types. What is essential in all contexts, however, is patient education – promoting vigilance for symptoms/signs of recurrence and self-directed engagement with health services. As a suggested guide to post-treatment monitoring of rarer ovarian cancer types, we advise employing BGCS-endorsed follow-up protocols – considering assigning patients at low-risk of recurrence (low grade /early stage; carcinoids) to 2 years of clinical follow-up; before either 3 years under telephone review or discharge to patient-initiated follow-up as most appropriate. For high-risk disease (high grade/advanced disease; clear cell; NECs) clinical follow-up for 3 years; combined with telephone consultations during years 4 and 5 is acceptable [24]. The value of tumour marker surveillance, in the author's opinion, should be individualised – dependent on serum level at diagnosis and trend during/response to treatment. In the context of secretory neuro-endocrine ovarian carcinomas, tumour-specific markers may perhaps yield greater benefit as a screening tool to diagnose relapse; as might consideration of surveillance CT or CT-PET.

Key Points

- The evidence base regarding rare ovarian histological subtypes is very limited compared to serous subtypes.
- These are, in general managed along similar lines to all epithelial ovarian cancers.
- The role of lymphadenectomy in MBTs and NECs is debatable
- Adjuvant treatment needs to be tailored to the underlying histology and (for NECs) may benefit from a specialist MDT opinion.

References

1. Chen RJ, Chen KY, Chang TC, Sheu BC, Chow SN, Huang SC. Prognosis and treatment of squamous cell carcinoma from a mature cystic teratoma of the ovary. J Formos Med Assoc. 2008;107(11):857–68.
2. Nasioudis D, Sisti G, Holcomb K, Kanninen T, Witkin SS. Malignant Brenner tumors of the ovary; a population-based analysis. Gynecol Oncol. 2016;142(1):44–9.
3. Anglesio MS, Wang YK, Maassen M, Horlings HM, Bashashati A, Senz J, et al. Synchronous endometrial and ovarian carcinomas: evidence of Clonality. J Natl Cancer Inst. 2016;108(6):djv428.
4. Blake Gilks C, Singh N. Synchronous carcinomas of endometrium and ovary: a pragmatic approach. Gynecol Oncol Rep. 2019;27:72–3.
5. Virarkar M, Vulasala SS, Morani AC, Waters R, Gopireddy DR, Kumar S, et al. Neuroendocrine neoplasms of the gynecologic tract. Cancers (Basel). 2022;14(7):1835.
6. Howitt BE, Kelly P, McCluggage WG. Pathology of neuroendocrine tumours of the female genital tract. Curr Oncol Rep. 2017;19(9):59.
7. Pang L, Guo Z. Primary neuroendocrine tumors of the ovary: management and outcomes. Cancer Med. 2021;10(23):8558–69.
8. Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014;124(1):1–5.
9. BGCS. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice 2017.
10. Winer I, Kim C, Gehrig P. Neuroendocrine tumors of the gynecologic tract update. Gynecol Oncol. 2021;162(1):210–9.
11. Fruscio R, Corso S, Ceppi L, Garavaglia D, Garbi A, Floriani I, et al. Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol. 2013;24(1):138–44.
12. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943–53.
13. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249–57.
14. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009;115(6):1234–44.
15. Hackethal A, Brueggmann D, Bohlmann MK, Franke FE, Tinneberg HR, Munstedt K. Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data. Lancet Oncol. 2008;9(12):1173–80.
16. Colombo N, Sessa C, Bois AD, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019.
17. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473–83.
18. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26):2484–96.
19. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.
20. Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391–402.
21. Harter P, Sehouli J, Vergote I, Ferron G, Reuss A, Meier W, et al. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. N Engl J Med. 2021;385(23):2123–31.
22. Coleman RL, Spirtos NM, Enserro D, Herzog TJ, Sabbatini P, Armstrong DK, et al. Secondary surgical

cytoreduction for recurrent ovarian cancer. N Engl J Med. 2019;381(20):1929–39.
23. Shi T, Zhu J, Feng Y, Tu D, Zhang Y, Zhang P, et al. Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):439–49.
24. Newton C, Nordin A, Rolland P, Ind T, Larsen-Disney P, Martin-Hirsch P, et al. British Gynaecological Cancer Society recommendations and guidance on patient-initiated follow-up (PIFU). Int J Gynecol Cancer. 2020;30(5):695–700.

Recurrent Ovarian Cancer

5

Bindiya Gupta and Kavita Singh

Introduction

Relapse is common with advanced ovarian cancer occurring in 50–90% of cases and majority will relapse in less than 5 years depending on the FIGO stage at diagnosis, use of neoadjuvant chemotherapy and extent of cytoreductive surgery. Recurrent ovarian cancer may be classified on the basis of response to platinum chemotherapy i.e. time from completion of chemotherapy till detection of relapse. Currently there are no predictive biomarkers for platinum resistance. Patients with advanced ovarian cancer with a treatment/platinum-free interval (TFI) of ≥6 months are defined as having **platinum-sensitive disease.** Recurrences occurring within 6 months of completing chemotherapy treatment, after an initial complete response is defined as **platinum resistant disease.** Patients who experience disease progression during frontline chemotherapy are considered **platinum refractory**. Platinum response also depends on the histology (mucinous ovarian cancer are usually platinum non responsive), performance status, prior chemotherapy etc. Recently instead of platinum resistance, according to ESMO-ESGO consensus meeting guidelines 2019, platinum non eligible ovarian cancer (PNEOC) patients are those who progress on or immediately after their last platinum based chemotherapy or have contraindications to platinum. Platinum eligible ovarian cancer (PEOC) includes all other cases of relapse.

Case 1

Age, Parity, PS	64 years, nulliparous ECOG = 0
Presenting complaints	**Follow up case of high grade serous ovarian** CA125 at initial presentation: 2500 IU/L Neoadjuvant chemotherapy (four cycle carboplatin + paclitaxel) and delayed debulking surgery (R0 resection); completed 3 cycles of adjuvant chemotherapy; BRCA negative Post treatment CA125: 32 U/L; regular follow up with 3 monthly CA125: Normal **Disease free interval:** 3 years **Presented** with non- specific backache
Co morbidities	Nil
CT scan followed by PETCT	No ascites, isolated para-aortic nodal recurrence 3 × 4 cm below the left renal vein
Other investigations	CA125: 164 U/L

B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_5

Case 2

Age, Parity, PS	70 years, P1 + 0 ECOG = 1
Presenting complaints	Diagnosed high grade serous ovarian cancer 4 years ago Underwent primary debulking surgery (R0 resection) + adjuvant chemotherapy × 6 cycles Post treatment CA125: Normal Follow up: Asymptomatic progressive rise in CA125
Co morbidities	Nil
CT scan followed by PETCT	No ascites, isolated diaphragmatic deposit on right side: 4 cm No liver, spleen, bowel, kidney, retroperitoneal disease No pelvic mass
Other investigations	CA125: Rising titres on follow up: 68 U/L, 235 U/L

Q. What Are the Diagnostic Pathways for Investigations in Suspected Recurrent Ovarian Cancer?

Recurrence of ovarian cancer can be suspected when there is a clinical suspicion or rising tumor marker on surveillance. Clinical presentation can vary according to the site of recurrence and may include symptoms like abdominal pain, palpable mass, urinary or bowel symptoms or symptoms of distant metastasis like backache, hemoptysis, seizures, jaundice etc. if there is a serial rise in the tumor marker (CA125) on follow up, in a patient with CA125 marker expressive ovarian cancer, warrants imaging to rule out recurrent disease. CA125 often rises several months before the clinical or symptomatic relapse. A significant rise of CA125 is considered if the concentration is twice the upper limit of normal 1 week apart. Initiation of early chemotherapy on basis of rising CA125 alone in absence of clinical or symptomatic relapse has not shown to offer any benefit in overall survival versus delayed chemotherapy when symptoms/clinical signs appear [1].

CT scan of the thorax, abdomen and pelvis is recommended for evaluation of recurrent disease with a reported accuracy of 70–92%. The main limitations are that small disease <5 mm is not detected, deposits on bowel serosa, mesentery and peritoneum can be missed especially in absence of ascites [2]. If facilities are available, it is recommended to perform a PET scan in order to rule out distant extra abdominal recurrences. In a meta-analysis of 34 studies, the pooled sensitivity and specificity for the detection of recurrent ovarian cancer was 79% and 84%, respectively, for CT, 75% and 78%, respectively, for MR imaging, and 91% and 88%, respectively, for PET/CT [3].

The false positivity of PET CT is high as it may also show high uptake in inflammation especially when interpreted within 6 months of surgery. Also, it is less sensitive for miliary peritoneal involvement, cystic or necrotic lesions, low grade, clear cell and mucinous tumours. It is also useful if CA125 levels are rising, patient is asymptomatic and conventional imaging is inconclusive or negative [4].A diagnostic laparoscopy can be performed to assess the feasibility of surgery in case of doubtful imaging; however, the assessment may be limited as a result of adhesions of previous surgery.

Q. What Is the Management Strategy for Recurrent Ovarian cancer?

The initial assessment to start treatment in recurrent ovarian cancer depends on the fitness of the patient and willingness for treatment. For platinum sensitive recurrent ovarian cancer, after the first relapse and a treatment free interval of more than 6 months, patients should be clinically **assessed for secondary debulking surgery**. In cases where the AGO score is positive (good performance status, ascites <500 ml, previous R0 resection), imaging suggests resectable disease, patient does not have major comorbidities, is willing for surgery and complete cytoreduction is achievable; secondary debulking surgery at a specialized oncology centre by an experienced surgical team should be performed [5].Surgery is followed by platinum based combination chemotherapy for six cycles with or without combination of bevacizumab or and PARP maintenance treatment. The latter is preferably used in BRCA positive patients. Both case 1 and 2 met the AGO score and complete cytoreduction was possible, hence secondary debulking was a good option.

Cytoreductive surgery in platinum-resistant disease, residual disease after primary surgery,

progressive disease during or within 6 months after primary chemotherapy is usually not indicated due to limited life expectancy and surgical morbidity/mortality [3].

When patients are not suitable for secondary cytoreduction, but have a platinum sensitive relapse in all probability, they are considered for **second line platinum based chemotherapy** for 6 months plus bevacizumab and/or PARP inhibitors, depending on the BRCA status. For initiation of chemotherapy, parameters like tumour biology, histology, previous chemotherapy, previous response to chemotherapy and toxicity profile, patient performance status, age, patient preference and current symptoms are taken into account. The platinum resistant or refractory group of patients should be offered a non platinum regimen with or without bevacizumab and therapy can be continued as long as the clinical efficacy is present with acceptable toxicity. In patients with BRCA mutations and platinum sensitive relapse, Rucaparib monotherapy or PARP maintenance can be considered. PARP inhibitors can even be given to patients who are potentially platinum sensitive and cannot tolerate bevacizumab irrespective of BRCA status.

Patients who are not suitable for chemotherapy, a **palliative care pathway** is adopted. Palliative care includes a combination of drugs, surgery, radiotherapy, psychological and Macmillan support. Palliative surgery is done to provide relief from pain, pressure symptoms and bowel conditions like acute abdomen, perforation or obstruction. Specialist cancer clinical nurse specialist are an integral part of support in providing care and act as a link between the patient and the medical care provider.

Q. What Are the Criteria for Secondary Debulking Surgery and What Are Its Contraindications?

Careful selection of patients is important for success of secondary debulking surgery in platinum sensitive recurrent ovarian cancer with a treatment free interval of 6 months. AGO score was developed and prospectively validated in the DESKTOP I and DESKTOP II trials respectively and helped to identify the cohort of patients who can undergo complete secondary cytoreduction to enhance overall survival and minimizing the surgical morbidity [6, 7]. The AGO criteria includes good performance status (ECOG 0), complete resection at initial cytoreductive surgery, and ascites <500 mL. The patient should be motivated and willing to undergo the surgical procedure and should not have major morbidities. Similar to the AGO score the SOC 1/SGOG investigators suggested the imodel score as shown in Table 5.1 [8].

Another factor that is important is the disease distribution at the time of recurrence when there is a high probability of complete resection. The aim of secondary debulking surgery is to achieve a R0 resection and both single site and multi site recurrences can be successfully treated as long as complete cytoreduction is achieved; although latter may be associated with reduced progression free survival (PFS) [8].

Surgery done at the high volume specialized oncology Centre with an experienced surgical team is the key to favourable outcome. There is lack of prospective studies regarding the role of HIPEC in recurrent ovarian cancer.

Recent trials that have addressed the outcomes of secondary debulking surgery and are discussed in Table 5.1.

Case 1

The patient underwent debulking of the para aortic nodes and received 6 cycles of adjuvant chemotherapy (Paclitaxel + carboplatin). The patient is on regular follow up for 2 years post secondary debulking surgery.

Case 2

The patient underwent right hemidiaphragm resection and reconstruction and received 6 cycles of adjuvant platinum based chemotherapy. The patient is on regular follow up for 4 years post secondary debulking surgery.

Table 5.1 Trials on secondary debulking surgery

Trial Name	Number of participants	Selection criteria for secondary debulking surgery	Outcomes	Comments
DESKTOP III 2020 [9]	407 patients	AGO criteria: Good performance status (ECOG[a] score: 0), ascites <500 ml, complete cytoreduction at initial surgery Platinum free interval of 6 months	Median overall survival (OS): With R0 resection: 53.7 months with surgery versus 46.2 months without surgery (Hazard ratio (HR) 0.76, 95% CI 0.59–0.97, $P = 0.03$) Median progression free survival (PFS): 18.4 months versus 14 months (HR: 0.66, 95%CI 0.54–0.82, $p < 0.001$)	Complete resection was achieved in 75% Patients with surgery and incomplete resection did worse (median 28.8 months) Grade 3/4 adverse events did not differ significantly between arms
SOC1/ SGOG-OV2 [10]	357 patients	Age at recurrence ≥18 years Platinum free interval of 6 months iMODEL score ≤4.7, including FIGO stage (0 or 0.8); residual disease after primary surgery (0 or 1.5); progression-free interval (0 or 2.4); PS ECOG (0 or 2.4); CA125 (0 or 1.8); and ascites at recurrence (0 or 3.0)	Median PFS was 17.4 m and 11.9 m in surgery and no surgery arm, respectively (HR 0.58, 95% CI 0.45–0.74, $p < 0.001$) The median accumulated treatment free survival (TFSa) was unreached and 39.5 m in R0 subgroup and no surgery arm, respectively (HR 0.59, 95%CI 0.38–0.91)	Complete resection (R0) rate was 76.7% in overall and 61.1% in pts. with iMODEL>4.7 Median time to start of first subsequent therapy (TFST) was 18.1 m vs 13.6 m in favor of the surgery arm (HR 0.59, 95%CI 0.46–0.76) Postoperative 30 d complication rate with ≥ grade 3 was 5.2%
GOG 213 [11]		Measurable platinum sensitive recurrent ovarian cancer deemed by the investigator to be suitable for complete gross resection	HR for death (surgery versus no surgery) was 1.29 Median OS 50.6 months and 64.7 months in surgery versus no surgery group respectively HR for disease progression was 0.82; 18.9 months versus 16.2 months in surgery versus no surgery group respectively	Complete gross resection achieved in 67% followed by platinum based chemotherapy with bevacizumab and bevacizumab maintenance

[a]Eastern Cooperative Oncology Group

Case 3

Age, Parity, PS	72 years, nulliparous ECOG = 0
Presenting complaints	**High grade serous ovarian cancer with platinum sensitive relapse** Primary debulking surgery (R0 resection); completed 6 cycles of adjuvant paclitaxel and carboplatin chemotherapy; BRCA negative **Disease free interval:** 2 years **Presented** with abdominal pain
Co morbidities	Nil
CT scan	Multi site recurrence: 1–2 cm nodes near coeliac axis, retroperitoneal nodal enlargement, omentum, vaginal vault mass (Fig. 5.1a–c)
Other investigations	CA125: 650 U/L

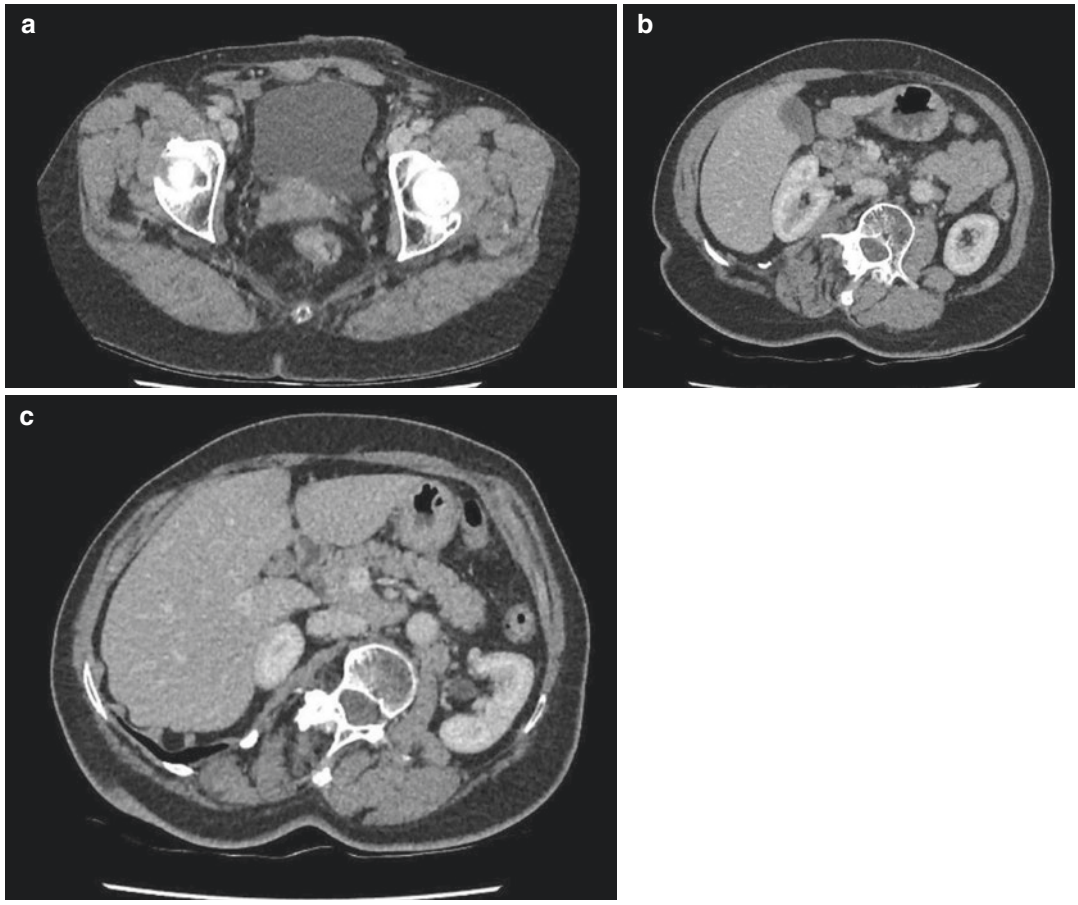


Fig. 5.1 (**a**) CECT showing vaginal vault recurrence (**b**) retroperitoneal nodal recurrence (**c**) celiac axis nodal recurrence

Q. What Are the Management Options for the Patient?

The above case has a multisite recurrence and does not satisfy the AGO criteria and complete cytoreduction is not feasible.

Platinum based chemotherapy alone or in combination with other agents like paclitaxel, gemcitabine, pegylated liposomal doxorubicin (PLD) given for six cycles is the treatment for platinum-sensitive recurrent EOC. When selecting single-agent versus combination therapy, it is important to consider the patient's performance status, serum albumin levels, disease volume, comorbidities, previous surgery, toxicity with previous therapy. Targeted agents like bevacizumab and PARP inhibitors may be added on an individual assessment basis.

The trials for chemotherapy for platinum sensitive disease are summarized in Table 5.2.

Table 5.2 Trials of chemotherapy in recurrent ovarian cancer

Trial name	Patient population	Methods	Outcomes	Comments
ICON4/ AGO-OVAR-2.2 [12]	Platinum-sensitive (n = 802)	Paclitaxel plus platinum chemotherapy versus single platinum-based chemotherapy	Paclitaxel + platinum combination versus platinum only group: 1. Difference in median survival of 5 months (29 vs 24 months in); HR 0.82 [95% CI 0.69–0.97], p = 0.02) 2. 2-year survival: 57 vs 50% 3. Median progression-free survival: 13 vs 10 months; hazard ratio 0.76 [0.66–0.89], p = 0.0004)	Higher incidences of grade 2 to 4 neurologic toxicity (20% vs 1%) and alopecia (86% vs 25%) with combination treatment
Intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG [13]	Platinum-sensitive (n = 356)	Six, 21-day cycles of carboplatin alone or carboplatin plus gemcitabine	Gemcitabine + carboplatin combination versus platinum only group Progression free survival: 8.6 months versus 5.8 months; HR, 0.72; 95% CI, 0.57–0.90; p = 0.003	Myelosuppression was significantly more common in the combination
CALYPSO trial	Platinum sensitive (n = 976)	Carboplatin and paclitaxel (CP) versus carboplatin and pegylated liposomal doxorubicin (PLD) (CD)	*CD arm versus CP arm* PFS: 11.3 versus 9.4 months, respectively (hazard ratio, 0.821; 95% CI, 0.72 to 0.94; P = .005) No statistically significant difference in overall survival	The PLD arm had fewer cases of severe (grade 3/4) neutropenia and neuropathy but more cases of severe thrombocytopenia

Q. Role of Antiangiogenic Targeted Therapy in Recurrent Ovarian Cancer?

Use of antiangiogenic targeted therapy depends on several patient factors like performance status, serum albumin levels, presence of co- morbidities like ischemic heart disease, hypertension, renal parameters, previous bowel resection, presence of anastomosis or colostomy. Careful selection of patients should be individualized and done before addition of anti-angiogenic targeted therapy in order to minimize treatment related toxicity.

In platinum sensitive recurrence, bevacizumab (15 mg/kg/every 3 weeks) in combination with platinum based second line chemotherapy with paclitaxel or gemcitabine followed by bevacizumab maintenance has shown improvement in PFS and can be recommended. In platinum resistant disease addition of bevacizumab in combination with second or third line platinum chemotherapy (weekly paclitaxel, liposomal doxorubicin or topotecan) may also be considered. The main trials are summarized in Table 5.3.

Table 5.3 Randomized trials on role of anti angiogenic drugs in recurrent epithelial ovarian cancer

Trial name	Patient population	Methods	Outcomes	Comments
ICON 6 [14]	Relapsed platinum sensitive; n = 486	Arm A; reference arm: Placebo alongside chemotherapy + placebo only maintenance Arm B; concurrent: Cediranib 20 mg once-daily with chemotherapy+ placebo only maintenance Arm C; maintenance: Cediranib 20 mg once-daily alongside chemotherapy + cediranib 20 mg once-daily maintenance	*Median progression-free survival* Arm C versus A: 11.0 months (95% CI 10.4–11.7) versus 8.7 months (7.7–9.4) (hazard ratio 0.56, 0.44–0.72, $p < 0.0001$) Arm B: Median progression-free survival was 9.9 months (95% CI 9.4–10.5); 90% had disease progression	Poor compliance with cediranib during maintenance treatment. Toxic effects like diarrohea, neutropenia, hypertension being the most common cause for discontinuation
OCEANS [15, 16]	Platinum-sensitive N = 484	Gemcitabine+ carboplatin(GC) + bevacizumab versus GC + placebo for 6–10 cycles; placebo or bevacizumab was then continued until disease progression	Bevacizumab versus placebo: median PFS 12.4 v 8.4 months, respectively (hazard ratio [HR], 0.484; 95% CI, 0.388 to 0.605; log-rank $P < 0.0001$) No significant difference in OS GC + bevacizumab: 33.6 months; GC + PL: 32.9 months	Grade 3 or higher toxicity, hypertension and proteinuria occurred more frequently in the BV arm 73% had died in a median follow up of 57–58 months
GOG 213 [17]	Platinum-sensitive N = 674	Standard chemotherapy (six 3-weekly cycles of paclitaxel [175 mg/m^2 of body surface area] and carboplatin [AUC 5] versus Same chemotherapy plus bevacizumab (15 mg/kg of bodyweight) every 3 weeks and continued as maintenance every 3 weeks until disease progression or unacceptable toxicity	Median overall survival in the chemotherapy plus bevacizumab group 42.2 months (95% CI 37.7–46.2) versus 37.3 months (32.6–39.7) in the chemotherapy group (hazard ratio [HR] 0.829; 95% CI 0.683–1.005; $p = 0.056$)	Grade 3 or worse adverse effects: 96% in chemotherapy + bevacizumab versus 86% chemotherapy group) including hypertension, proteinuria
AURELIA [18]	Platinum resistant (n = 361)	Single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal	Median PFS: 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy. Overall survival:13.3 with chemotherapy alone versus 16.6 months with bevacizumab (HR 0.85 (95% CI, 0.66 to 1.08); $P < 0.174$)	Toxicity more common with bevacizumab, gastrointestinal perforation in 2.2%

Q. What Is the Role of Poly (Adenosine Diphosphate Ribose) Polymerases (PARP) Inhibitor as Targeted Therapy?

Following second-line chemotherapy, PARP inhibitors (olaparib, niraparib, rucaparib) may be given as maintenance therapy up to 5 years following a response to platinum based second or higher line of treatment. The benefit is maximum in BRCA mutated patients and least in HRD negative patients. PARP inhibitors (rucaparib and olaparib) may also be given as monotherapy in BRCA mutation patients. FDA has approved olparib, rucaparib and niraparib as maintenance therapy for recurrent ovarian cancer irrespective of BRCA status [19].Toxicity with PARP inhibitors is generally manageable with dose reductions and interruption in therapy. Combination of antiangiogenic drugs and PARP inhibitors is not proven and trials are ongoing.

The trials are summarized in Table 5.4.

Table 5.4 Randomized trials of PARP inhibitors in recurrent epithelial ovarian cancer

Trial name	Patient population	Methods	Outcomes	Comments
Study 19 [20]	Received two or more courses of platinum-based chemotherapy with response (N = 265)	Oral maintenance olaparib (as capsules; 400 mg twice a day) or a matching placebo	Olaparib versus placebo PFS (BRCA m): 11.2 months versus 4.3 months; $P < 0.001$ PFS (BRCA wild type): 7.4 months versus 5.5 months; $P < 0.0075$ Overall survival: 29.8 months vs 27.8 months; p = NS BRCAm:34.9 months vs 30.2 months	No major grade 3 toxicity in Olaparib group
SOLO-2 [21]	Platinum-sensitive, relapsed ovarian cancer patients with a BRCA1/2 mutation, aged 18 years or older, ECOG score of 0–1	Olaparib300 mg or matching placebo tablets	Median progression-free survival: 19.1 months [95% CI 16.3–25.7] with olaparib versus 5.5 months [5.2–5.8] with placebo; hazard ratio [HR] 0.30 [95% CI 0.22–0.41], p < 0.0001) OS: (51.7 months with olaparib vs 38.8 months with placebo; hazard ratio, 0.74; $P = 0.054$). At 5 years' follow-up, 42.1% of women taking olaparib were alive, vs 33.2% taking placebo	Main side effect with olaparib was anemia. Toxicities with olaparib were low grade and manageable

Table 5.4 (continued)

Trial name	Patient population	Methods	Outcomes	Comments
ENGOT-OV16/ NOVA trial [22]	N = 553	Presence or absence of a germline BRCA mutation (gBRCA cohort and non-gBRCA cohort) and the type of non-gBRCA mutation and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily	Median duration of progression-free survival: Niraparib versus placebo; 21.0 vs. 5.5 months in the gBRCA cohort (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41), as compared with 12.9 months vs. 3.8 months in the non-gBRCA cohort for patients who had tumors with homologous recombination deficiency (HRD) (hazard ratio, 0.38; 95% CI, 0.24 to 0.59) and 9.3 months vs. 3.9 months in the overall non-gBRCA cohort (hazard ratio, 0.45; 95% CI, 0.34 to 0.61; P < 0.001 for all three comparisons)	The most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (in 19.6%), which were managed with dose modifications
ARIEL2 [23]	Recurrent, platinum-sensitive, high-grade ovarian carcinoma (n = 206)	Three groups: BRCA mutant, BRCA wild-type and LOH high, or BRCA wild-type and LOH low Oral rucaparib at 600 mg twice per day for continuous 28 day cycles until disease progression or any other reason for discontinuation	Median progression-free survival: BRCA mutant: 12.8 months (95% CI 9.0–14.7) BRCA wild-type and LOH high: 5.7 months (5.3–7.6) BRCA wild-type and LOH low: 5.2 months (3.6–5.5)	Anemia and deranged liver function most common side effects
SOLO 3 [24, 25]	Germline BRCA-mutated platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy N = 266	Olaparib 300 mg twice a day versus single-agent nonplatinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan)	*Olaparib versus chemotherapy* • Median PFS: 13.4 *v* 9.2 months; hazard ratio, 0.62 [95% CI, 0.43 to 0.91]; *P* = 0.013 • Objective response rate: 72.2% *v* 51.4%; *P* = 0.002	

Q. What Is the Role of Immune Therapy in Recurrent Ovarian Cancer?

Immune therapy is emerging as a targeted therapy for recurrent epithelial ovarian cancer and several trials have been conducted and ongoing investigating the roles of drugs like nivolumab, pembrolizumab, avelumab. Combination trials of niraparib and pembrolizumab showed signs of efficacy in patients with platinum-resistant recurrent EOC.

Case 3 4 cycles of carboplatin and liposomal doxorubicin was given to the patient. Repeat CT scan shows decrease in nodal mass 2 cm, and

mesenteric nodule to 2 cm with haziness in few more areas suggestive of partial response. Chemotherapy was continued for two more cycles and repeat PET CT is planned to assess response.

Key Points

1. The initial assessment to start treatment in recurrent ovarian cancer depends on the fitness of the patient and willingness for treatment.
2. Patients should be clinically assessed for secondary debulking surgery using clinical discretion in oligo metastatic disease, isolated pelvic recurrence where complete cytoreduction is achievable**.** AGO score and iModel scores are good predictors of suitability of SDS.
3. Surgery is followed by platinum best combination chemotherapy for six cycles with or without combination of bevacizumab or and PARP maintenance treatment.
4. When patients are not suitable for secondary cytoreduction, but have a platinum sensitive relapse in all probability, they are considered for **second line platinum based chemotherapy** for 6 months plus Bevacizumab and/or PARP inhibitors.
5. The platinum resistant or refractory group of patients should be offered a non platinum regimen with or without bevacizumab and therapy can be continued as long as the clinical efficacy is present with acceptable toxicity.
6. Patients who are not suitable for chemotherapy, a **palliative care pathway** is adopted.

References

1. Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, Kristensen G, Mediola C, Coens C, Qian W, Parmar MK, Swart AM. MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010;376(9747):1155–63.
2. Manganaro L, Gigli S, Antonelli A, et al. Imaging strategy in recurrent ovarian cancer: a practical review. Abdom Radiol. 2019;44:1091–102.
3. Gu P, Pan LL, Wu SQ, et al. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a sys- tematic review and meta-analysis. Eur J Radiol. 2009;71:164–17.
4. Zimny M, Siggelkow W, Schröder W, et al. 2-[Fluorine-18]- fluoro-2-deoxy-D-glucose positron emission tomography in the diagnosis of recurrent ovarian cancer. Gynecol Oncol. 2001;83:310–5.
5. Bommert M, Harter P, Heitz F, du Bois A. When should surgery be used for recurrent ovarian carcinoma? Clin Oncol (R Coll Radiol). 2018;30(8):493–7.
6. Harter P, du Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, Gropp M, Huober J, Fink D, Schröder W, Muenstedt K, Schmalfeldt B, Emons G, Pfisterer J, Wollschlaeger K, Meerpohl HG, Breitbach GP, Tanner B, Sehouli J. Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Committee; AGO Ovarian Cancer Study Group. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol. 2006;13(12):1702–10.
7. Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer. 2011;21(2):289–95.
8. Kumar S, Srinivasan A, Phillips A, Madhupriya R, Pascoe J, Nevin J, Elattar A, Balega J, Cummins C, Sundar S, Kehoe ST, Singh K. Does sites of recurrence impact survival in secondary cytoreduction surgery for recurrent epithelial ovarian cancer? J Obstet Gynaecol. 2020;40(6):849–55.
9. Du Bois A, Sehouli J, Vergote I, Ferron G, Reuss A, et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of AGO DESKTOP III/ENGOT-ov20. Available at: https://meetinglibrary.asco.org/record/185438/abstract. Accessed 29 June 2020.
10. Zang R, Zhu J, Shi T, Liu J, Tu D, Yin S, et al. A randomized phase III trial of secondary cytoreductive surgery in later recurrent ovarian cancer: SOC1/SGOG-OV2. Available at: https://meetinglibrary.asco.org/record/185448/abstract. Accessed 4 June 2022.
11. Coleman RL, Spirtos NM, Enserro D, Herzog TJ, Sabbatini P, Armstrong DK, et al. Secondary surgical Cytoreduction for recurrent ovarian cancer. N Engl J Med. 2019;381(20):1929–39.
12. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, et al. ICON and AGO collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian

cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003;361(9375):2099–106.
13. Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, et al. AGO-OVAR; NCIC CTG; EORTC GCG. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006;24(29):4699–707.
14. Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJS, et al. ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;387(10023):1066–74. https://doi.org/10.1016/S0140-6736(15)01167-8. Erratum in: Lancet. 2016 Apr 23;387(10029):1722.
15. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30(17):2039–45.
16. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10–6.
17. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(6):779–91.
18. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302–8.
19. Current approval for PARP inhibitors. Available at: oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/parp-inhibition-and-dna-damage-response-ddr/parp-inhibitors/clinical-activity/ovarian-cancer/current-approvals. Accessed on 14 June 22.
20. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016;17(11):1579–89.
21. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. SOLO2/ENGOT-Ov21 investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274–84.
22. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. ENGOT-OV16/NOVA investigators. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–64.
23. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol. 2017;18(1):75–87.
24. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA 3rd, Bidziński M, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol. 2020;38(11):1164–74.
25. https://meetinglibrary.asco.org/record/185419/abstract.

Platinum Resistant Ovarian Cancer

6

Kavita Singh and Bindiya Gupta

Introduction

Response to treatment for ovarian cancer is assessed by combination of clinical response, imaging and tumor marker CA125. It is classified as **complete response** when there is no clinical, biochemical or radiological evidence of disease after completion of therapy. The response is **partial** if the tumor does not undergo complete resolution on imaging and CA125 remains high but is reduced compared to previous levels. If CT scan findings in association with CA125 remains same it is called **stable** response or when findings on CT scan imaging worsen in association with increase in CA125 with or without clinical symptoms it is called **progressive disease**.

Surveillance of patients after treatment completion is usually done on the basis of clinical symptoms, CA125 and imaging (CT scan is done if the patient is symptomatic). Serum CA125 concentration often rises several months before clinical or symptomatic relapse. This poses a major challenge in patient management as there is a lack of survival benefit with early treatment of relapse on the basis of a raised CA125 concentration alone [1]. Therefore, the value of routine measurement of CA125 for follow up after complete response is not proven.

About 70–85% of patients with epithelial ovarian cancer relapse and median survival for patients with recurrent disease ranges from 12 months to 24 months [2]. This depends on the FIGO stage at diagnosis, use of neoadjuvant chemotherapy and extent of cytoreductive surgery. Recurrent ovarian cancer may be classified on the basis of response to platinum chemotherapy i.e. time from completion of chemotherapy till detection of relapse (Fig. 6.1) [3]. Patients with a platinum-free interval (PFI) of ≥6 months are defined as having **platinum-sensitive disease.** It is further classified as **partial sensitive** when the treatment free interval is between 6–12 months and **sensitive** when PFI is >12 months. **Platinum resistant disease** is defined as recurrence within 6 months after an initial complete response. Cases which do not achieve a complete response, experience disease progression during frontline therapy or relapse within 1 month of treatment completion are considered **platinum refractory**.

At the fifth Ovarian cancer consensus conference it was proposed that the term Platinum free interval (PFI) may be replaced with TFI (Treatment free interval). The platinum free interval usually signifies primary platinum resistance and this is less useful after more than one relapse, after use of non-platinum agents and after discontinuation of maintenance therapy

K. Singh (✉)
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_6

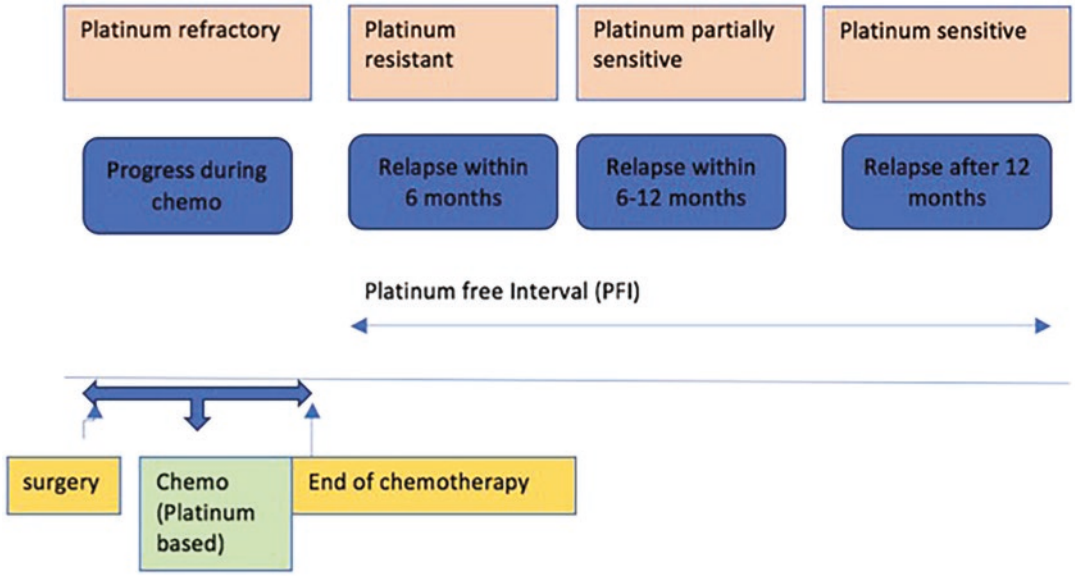


Fig. 6.1 Definition of platinum resistant and sensitive ovarian cancer

with bevacizumab and PARP inhibitors. Moreover, follow up protocols i.e. use of CA125, CT scan or PET CT are done at variable intervals and may influence the time of detection of relapse. Hence they have proposed that it can be redefined as Treatment free interval-platinum therapy (TFIp), Treatment free interval non-platinum drugs (TFInp) or treatment free intervals on biological therapy or targeted therapy (TFIb).

Platinum resistance can be classified as primary or secondary. Primary platinum resistance is a condition that is intrinsic to the tumour, occurs during first line chemotherapy leads to progressive disease during or immediately after therapy. Secondary or acquired platinum resistance occur after an initial response to platinum therapy. The incidence of platinum resistant disease is 25% although eventually majority become platinum resistant after multiple relapses [4]. Platinum free interval is the most important predictor of response to subsequent lines of chemotherapy and the most important prognostic factor for PFS and OS. The longer the PFI, the higher the response rate (RR) and longer the duration of response to secondary therapy. Upon recurrence in EOC, the choice of second-line chemotherapy is guided by platinum-free interval (PFI) [5].

Case1: Stage 4a/b High Grade Serous Ovarian Cancer (Pleural Effusion/Hilar Lymph Nodes)

Age, PS	52 years, nulliparous, ECOG −1
Presenting complaints	Abdominal distension, loss of appetite
Co morbidities	Hypertension (controlled)
CECT abdomen and pelvis	
Image guided biopsy	**High grade serous ovarian cancer CK7+ve, CK 20 negative, P53 aberrant (+ve)**
Tumor markers	CA125: 4323 KU/L, CEA: 2, CA19–9: 25
Surgery	**Neoadjuvant chemotherapy (carboplatin + paclitaxel)** **CA-125 levels** After first cycle: 2000 KU/L After second cycle: 93 KU/L After third cycle: 200 KU/L After fourth cycle: 383 KU/L After fifth cycle: 686 KU/L
CT scan thorax, abdomen and pelvis (after 3 cycles of chemotherapy)	Resolution of ascites and pleural effusion. Marginal increase in the size of the hi hilar nodes, peritoneal thickening, nodules seen on diaphragm. Omental cake p present, ovarian masses unchanged
BRCA test	Negative

Q. What Are the Mechanisms of Platinum Resistance?

Ovarian cancer has a heterogenous cell population and express variable carboplatin sensitivity within the same tumor with both carboplatin resistant and sensitive clones. The various mechanisms proposed for platinum resistance are as follows [6]:

1. **Presence of intrinsically resistant cancer cells:** Minor subpopulations of intrinsically resistant cell clones already pre-exist and undergo numerous cell divisions before clinical presentation. This hypothesis is supported by the fact that residual disease after surgery is the strongest prognostic factor for survival.
2. **Acquired drug resistance** emerges during treatment as a result of high genomic instability in HGSOC. Increased residual tumor mass implies a higher tumor cell load, which increases the chances of acquired drug resistant subclones. **Molecular mechanisms** including alteration in intracellular transport of cisplatin, aberrant DNA methylation etc. have been identified but do not have translational relevance for the clinical setting.
3. **Proteomics** will pave way in future to identify platinum resistance and is only experimental. Proteins like RELA and STAT5B may have a clinical significance in future but are only experimental at the moment.

Q. What Are the Biomarkers or Predictors of Platinum Resistance?

There are no validated predictive markers for platinum resistance. There are certain factors which may influence the response to chemotherapy and platinum free interval [7].

1. **Tumor histology:** Certain tumors like mucinous, clear cell and low grade serous are considered less responsive to first line chemotherapy containing carboplatin. High grade tumors are more chemoresponsive.
2. **BRCA 1/BRCA 2 and other homologous recombinant mutations:** Studies have shown that BRCA mutations are associated with better survival outcomes which likely reflects increased response rates to platinum based chemotherapy. Somatic mutations in other homologous recombinant genes may also have a similar impact on overall survival and platinum responsiveness.
3. **Performance score:** Patients with poor physical function, low baseline global health status and quality of life and early onset side effects of chemotherapy may discontinue treatment resulting in treatment failure [8]. This sub population represents poor chemotherapy response not necessarily related to tumor resistance.
4. **Use of maintenance treatment with Bevacizumab, PARP inhibitors** also influence the response to chemotherapy and treatment free interval as they have their own influence in prolonging PFI/TFI and these may mask a true platinum resistance by delaying in manifestation of recurrence.

Q. What is the Recommended Treatment for Platinum Resistant Ovarian Cancer?

The average overall survival of platinum resistant ovarian cancer is usually 10–12 months. Hence, the main objective of treatment for this group becomes palliative i.e. to control symptoms, enhance and maintain quality of life and minimize side effects of any second line chemotherapy. The choice of agent for individual patient depends on the history of prior treatment, residual toxicities, availability of the drug, cost, convenience of treatment and patient preferences.

In patients with *Primary platinum resistance* i.e. progression on first platinum based therapy, early symptomatic relapse and platinum intolerability; repeat therapy with platinum is not a good option. Phase III trials have shown that sequential monotherapy with non-platinum agents is preferred in this group of patients. Dugs commonly used are Paclitaxel (Response rate

22–30%) [9], Topotecan (5.9–18%) [10], pegylated liposomal doxorubicin (response rate 8–16%), Gemcitabine (response rate: 14–22%) [11] and etoposide (response rate 25%) [12].

The addition of bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression or unacceptable toxicity to single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) showed prolongation in PFS (3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy), although without any significant benefit on overall survival. It was also associated with improvement in abdominal symptoms and reduction in ascites [13]. Adverse effects related to Bevacizumab are hypertension, proteinuria, hemorrhage, thrombosis and bowel perforation.

The addition of PARP inhibitors (Olaparib 400 mg twice daily) in BRCA positive platinum resistant ovarian cancer has been shown to be effective with response rate of 30% and overall survival of 16.6 months [14]. However, PARP inhibitors are not recommended routinely for platinum resistant relapse.

In *secondary or acquired* resistance, in patients who had a prior response to platinum, a platinum re-challenge may be considered with or without addition of Bevacizumab. In this group of patients, one of the protocols practiced to overcome carboplatin resistance is to use liposomal doxorubicin after first relapse for 6 cycles, and if disease remains stable the carboplatin rechallenge is given. This protocol attempts to prolong the time interval between completion of last platinum chemotherapy and platinum rechallenge, in order to cross over from a platinum resistant tumor to partial platinum sensitivity and has shown favourable outcomes (unpublished data).

Hormone therapy has a role in low grade serous cancers but its role in high grade serous cancer is not clearly established. It may be effective in a subset of patients with hormone receptor positive status and has the advantage of less side effects.

Studies are ongoing to establish the role of immune checkpoint inhibitors (anti PD-1 inhibitor pembrolizumab, avelumab), Anti VEGF tyrosine kinase inhibitors (pazopanib, cediranib) and epigenetic therapies to restore platinum sensitivity either as standalone treatments or in combination [15, 16].

The initial response, in the present case to first two cycles was very good, however CA125 started to rise after the third cycle. Radiological response was partial with only resolution of ascites and pleural effusion.

The patient was counselled regarding the partial response to chemotherapy and the possibility of platinum resistance and was given the option of completion of six cycles and maintenance therapy with bevacizumab and another option of a diagnostic laparoscopy to assess suitability for proceeding to debulking surgery and possibility of complete or optimal cytoreduction. The patient preferred to choose the second option and underwent a diagnostic laparoscopy with biopsy.

Intraoperative findings:

Miliary disease on the small bowel and mesentery, disease on the undersurface of diaphragm and omental cake.

BRCA testing (germline + somatic): negative.

Treatment plan: Completion of six cycles of carboplatin and paclitaxel followed by bevacizumab maintenance treatment.

Key Points

1. Carboplatin resistance is seen in 25% of epithelial ovarian and is more commonly seen in mucinous, clear cell and low grade serous ovarian cancer
2. Primary platinum resistance is intrinsic to the tumour and has poor outcome. Secondary or acquired platinum resistance occurs after an initial response to platinum therapy and is invariably seen in all EOC recurrences. Secondary resistance has a better outcome than primary resistance.

3. BRCA 1/2 mutation are usually platinum sensitive with low incidence of platinum resistance
4. Single agent non platinum chemotherapy is used for treatment with an overall response rate of 25%. Addition of Bevacizumab in selected population to second line chemotherapy has shown benefit in overall survival benefit of 4–5 months.
5. PARP inhibitors are not favored for refractory or resistant disease, however Olaparib shows some response in BRCA positive platinum resistant patients.

References

1. Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, Kristensen G, Mediola C, Coens C, Qian W, Parmar MK, Swart AM. MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010;376(9747):1155–63.
2. Chuang YT, Chang CL. Extending platinum-free interval in partially platinum-sensitive recurrent ovarian cancer by a non-platinum regimen: its possible clinical significance. Taiwan J Obstet Gynecol. 2012;51(3):336–41.
3. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth ovarian cancer consensus conference for the gynecological cancer intergroup; recurrent disease. Ann Oncol. 2017;28:727–32.
4. Ushijima K. Treatment for recurrent ovarian cancer-at first relapse. J Oncol. 2010;2010:497429.
5. Gupta S, Nag S, Aggarwal S, Rauthan A, Warrier N. Maintenance therapy for recurrent epithelial ovarian cancer: current therapies and future perspectives - a review. J Ovarian Res. 2019;12(1):103.
6. Alkema NG, Wisman GB, van der Zee AG, van Vugt MA, de Jong S. Studying platinum sensitivity and resistance in high-grade serous ovarian cancer: different models for different questions. Drug Resist Updat. 2016;24:55–69.
7. Pujade-Lauraine E, Banerjee S, Pignata S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. J Clin Oncol. 2019;37(27):2437–48.
8. Oncolato FT, Joly F, O'Connell R, Lanceley A, Hilpert F, Buizen L, et al. GCIG Symptom Benefit group. Reducing uncertainty: predictors of stopping chemotherapy early and shortened survival time in platinum resistant/refractory ovarian cancer-the GCIG symptom benefit study. Oncologist. 2017;22(9):1117–24.
9. Markman M, Hall J, Spitz D, et al. Phase II trial of weekly single agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. J Clin Oncol. 2002;20:2365–9.
10. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol. 1997;15:2183–93.
11. Oronsky B, Ray CM, Spira AI, Trepel JB, Carter CA, Cottrill HM. A brief review of the management of platinum-resistant–platinum-refractory ovarian cancer. Med Oncol. 2017;34:103.
12. Ganghadaran SGD. Management of platinum resistant—refractory ovarian cancer: a short review. J Cancer Res Treat. 2016;4(2):32–6.
13. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302–8.
14. Kim G, et al. FDA approval summary: olaparib monotherapy inpatients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. Clin Cancer Res. 2015;21(19):4257–61.
15. Indini A, Nigro O, Lengyel CG, Ghidini M, Petrillo A, Lopez S, et al. Immune checkpoint inhibitors in platinum resistant ovarian cancers. Cancers (Basel). 2021;13(7):1663.
16. Marchetti C, Palaia I, De Felice F, Musella A, Donfracesco C, Vertechy L, Romito A, Piacenti I, Musio D, Muzii L, Tombolini V, Benedetti Panici P. Tyrosine-kinases inhibitors in recurrent platinum-resistant ovarian cancer patients. Cancer Treat Rev. 2016;42:41–6.

Metastatic Ovarian Cancer

7

Anastasios Tranoulis

Introduction

Krukenbergtumour (KT) is a rare metastatic signet ring cell ovarian tumour (OT), accounting for 1–2% of all OTs [1]. The stomach is the primary site in the majority of KTs, followed by colorectal (CRC), appendiceal and breast carcinomas (BC), particularly invasive lobular carcinoma [1]. KTs are characterised by uncertain pathogenesis, challenging etiological diagnosis and poorer prognosis vis-a-vis their primaries. According to Novak and Gray diagnostic criteria, a mucin-secreting signet ring cell carcinoma in the dense fibroblastic ovarian stroma is referred to as KT [2]. The presence of the following characteristics is required for diagnosis: stromal involvement, mucin-producing neoplastic signet ring cells and ovarian stromal sarcomatoid proliferation [3].

The treatment approach to KT remains controversial and depends mainly upon the primary origin and the dissemination of the tumour. To date, treatment mainly consists of ovarian metastasectomy, chemotherapy or radiotherapy; however, the optimal treatment has not yet been established. The prognosis is generally poor and depends upon the primary origin of the tumour. The median overall survival (OS) for KTs of breast, colorectal and gastric primary origin has been reported to be 31, 22 and 11 months, respectively [4].

A. Tranoulis (✉)
Department of Gynaecological Oncology, The Pan-Birmingham Gynaecological Cancer Centre, Birmingham City Hospital, Birmingham, UK
e-mail: Anastasios.tranoulis1@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_7

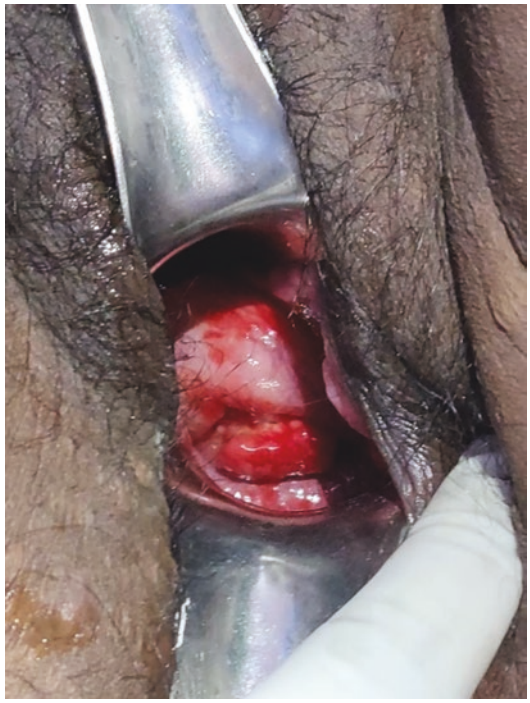


Fig. 7.1 Growth present on the posterior lip of cervix

Case Scenarios

Case Scenario 1

Age, Parity, PS	32 years, P3+0, ECOG 2, BMI -21
Clinical presentation	Abdominal distension × 4 months (progressively increasing) Loss of appetite, constipation M/H: Prolonged cycles 2–3 days/2–3 months × 5 years Amenorrhea x1 ½ years; One episode of spotting in December 2021 Examination (Fig. 7.1) P/A: Grossly distended abdomen-34 weeks size enlarged masses (two separate masses felt), fluid thrill+, no hepato-splenomegaly Pelvic examination: Fleshy growth on post lip of cervix 2 × 3 cm, anterior cervical lip app normal, bleeding on touch, vagina normal, post fornix thickened POD puckered no nodularity, right parametrium minimal thickening
Co morbidities	Nil
Cervical biopsy	Invasive mucinous carcinoma cervix CK 7 positive, CK20 negative, WT1 –ve, P16 –VE, CEA +VE
MRI	Heterogeneous enhancing mass seen in endocervical canal in posterior lip of cervix, complex solid cystic lesion in B/L adnexa. Increased omental fat stranding and caking in left paracolic gutter. Splenomegaly Impression: Possible Primary ovarian or metastatic/Krukenberg ovarian tumor
PET CT	Metabolically active lobulated solid cystic mass lesions in bilateral adnexa, omental stranding mild ascites metabolically active soft tissue density lesion in cervix and lower uterine segment likely neoplastic, FDG avid para-aortic lymph nodes, aorto-caval and retro-caval nodes (1.5–2 cm)
Other investigations	CA125: 136 U/L, CA19-9: 59 U/ml, CEA: 12 ng/mL Hb: 12.3gm%, LFT/ KFT: Normal Upper GI endoscopy: Hiatus hernia, antral gastritis Lower GI endoscopy: Normal

Q. What Is the Management Plan?

This is rare case of invasive cervical mucinous adenocarcinoma (CMA) with bilateral complex adnexal masses and possible para-aortic lymph node (PaLN) and omental involvement. The upper and lower gastro-intestinal (GI) endoscopy tests have ruled out the possibility of GI metastasis. MRI of the pancreas was also unremarkable. In this case, there are two possible clinical scenarios: i. metastatic CMA, ii. invasive CMA with synchronous primary tubo-ovarian carcinoma. Tumour markers are often helpful in differential diagnosis. CMA can present with elevated serum levels CA199 and normal levels of CA125 and CEA, whilst serum CEA is highly expressed in primary ovarian or GI metastatic CMA [5, 6]. The gold standard diagnostic modality in such cases is the image-guided biopsy (e.g., omental biopsy) or diagnostic laparoscopy with biopsies, which would

also give more information concerning the dissemination of the disease.

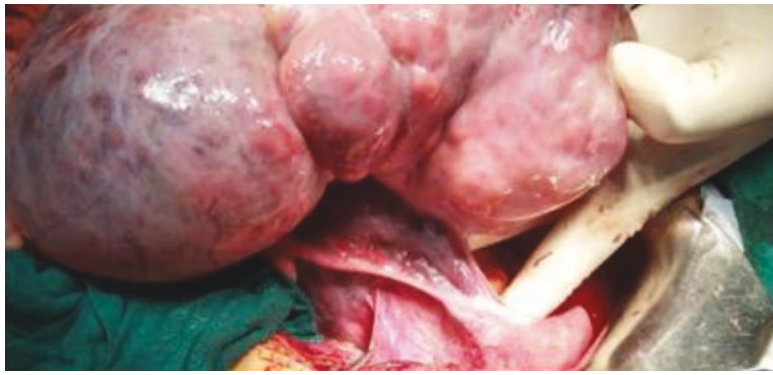
In case of synchronous invasive CMA (FIGO stage IB2) and advanced tubo-ovarian carcinoma (FIGO stage IIIC), a type C1 radical hysterectomy, pelvic lymphadenectomy, and cytoreductive surgery (including the bulky PaLNs) with a view to achieve R0 excision followed by adjuvant chemotherapy (carboplatin and placlitaxel) is the treatment of choice. The addition of adjuvant radiotherapy depends upon the presence of intermediate- or high-risk factors, yet, owing to the aggressive behaviour of mucinous cervical carcinoma-especially the gastric type-adjuvant radiotherapy (RT) is usually recommended [7]. Nonetheless, CMA is characterized by marked chemotherapy and radiotherapy-resistance [8–10].

In case of metastatic CMA the overall prognosis is poor and the optimal treatment management is not established [8–10]. The treatment management is based upon the findings of image-guided biopsy (e.g. omental biopsy) or intraoperative frozen section (PaLN dissection, omental biopsy, adnexectomy). The resection of ovarian metastatic lesions is seemingly one of the key elements to survival. Tumour-load reduction appears to improve overall survival owing to their poor response to chemotherapy or radiotherapy [9, 10]. Aim of surgery is to obtain macroscopic clearance and depending upon tumour size and spread may require a simple or radical hysterectomy [8]. In case of pelvis-confined disease, surgical resection and adjuvant concomitant chemoradiotherapy is the treatment of choice [8–10]. In case of PaLND involvement, radiosensitising chemotherapy with extended-field radiotherapy should be administered [8–10]. Finally, in case of disseminated disease (e.g. peritoneal or omental involvement) chemotherapy is the treatment of choice [8–10]. For locally-advanced or advanced stage CMA the role of hysterectomy or debulking surgery (low volume disease) remains controversial, though, there is some evidence arising from small case series, that surgery is likely to improve overall prognosis as other modalities of treatments like chemotherapy and radiotherapy are less effective [8–10].

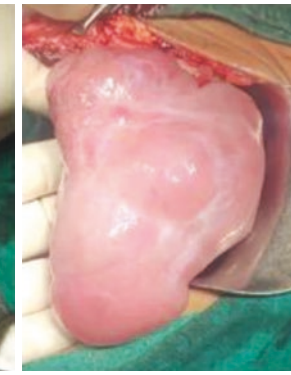
Q. What Are the Tests to Differentiate Two Primary Malignancies Versus a Metastatic Tumour to the Ovary from the Cervix?

CMA can present with elevated serum levels CA199 and normal levels of CA125 and CEA, whilst serum CEA is highly expressed in primary ovarian or gastrointestinal metastatic mucinous adenocarcinoma [5, 6]. The model proposed by Seidman et al. can also assist in the differentiation of ovarian primary and CMA [11]. Based upon this algorithm, bilateral ovarian masses of any size or unilateral ovarian masses with diameters $\leq$10 cm are metastatic, while unilateral ovarian masses with diameters >10 cm are primary mucinous adenocarcinomas.

The pathological and immunohistochemical (IHC) analysis of cervix and ovaries after surgery or pre-treatment biopsy (e.g., omental or peritoneal image-guided biopsy) represents the gold standard diagnostic modality in such cases. KTs of mucinous cervical origin commonly express oestrogen/progesterone receptors (ER)/(PR), cytokeratin 20 (CK20) and CEA negatively, but protein 53 (p53) and cytokeratin 7 (CK7) positivity [10, 12, 13]. Interestingly, although CMA are HPV-negative, approximately 50% of these still demonstrate protein 16 (p16) positivity, which can be used as an important IHC factor for differentiating the cervical origin of KTs. In this case, the cervical tumour demonstrated both HPV and p16 results according to IHC staining; notwithstanding, (HPV) infection and p16 IHC are typically negative in gastric type cervical adenocarcinoma [10, 12, 13].



Right ovarian mass



Left ovarian mass

Fig. 7.2 Krukenberg tumor

Case Scenario 2

Age, Parity, PS	18 years, single, ECOG 2, BMI -19
Clinical presentation	Abdominal distension × 6 months (progressively increasing) Pain abdomen × 6 months Menstrual cycles regular Examination: Firm to hard mas measuring 32 weeks size gravid uterus with restricted mobility, nodularity in pouch of Douglas
Co morbidities	Nil
X Ray	Right side pleural effusion
CECT chest + abdomen + pelvis	10 × 20 × 17 cm mass with larger component towards the right hemi-pelvis, close to the anterior abdominal wall arising from bilateral adnexa. Uterus normal, multiple enlarged enhancing para aortic lymph nodes, liver small granuloma of size 1 cm in segment VIII. Spleen, pancreas normal. Minimal omental stranding present. Right pleural effusion
Other investigations	CA125: 148 U/L, CA19-9: 1843 U/ml, CEA: 5.36 ng/ml, BhCG-2.3 mIU/ml, AFP 2 ng/ml, LDH: 162 IU/L Hb: 12.3gm%, LFT/ KFT: Normal Upper GI endoscopy: Erosive gastritis Lower GI endoscopy: Normal
PET CT scan	FDG avid masses arising from bilateral adnexa likely malignant. Multiple Para-aortic and aorto-caval nodes show FDG uptake. No other FDG positive area seen elsewhere
Surgery	Total abdominal hysterectomy + bilateral salpingo-oophorectomy + appendicectomy + Para-aortic lymphadenectomy + supra-colic omentectomy Frozen section: Malignant adenocarcinoma
Intraoperative findings (Fig. 7.2)	Right ovarian mass 20 × 10 cm, left ovarian mass 10 × 8 cm, capsule intact, uterus cervix normal, para-aortic and aorto-caval nodes enlarged 4 × 3 cm, 1 cm nodule in omentum, rest normal
Histopathology	Bilateral ovaries multiple tumor deposits both in glandular architecture and solid sheets, spindling is also noted, signet ring cells +, LVSI, intraluminal mucin in occasional tumor cells, metastatic deposits in fallopian tubes with submucosal spread, omentum positive Paraaortic nodes positive (5/12), tubercular lymphadenitis noted Appendix, uterus, cervix normal IHC: CK7 positive, CK 20 positive Impression: Krukenberg tumor, metastatic deposits in fallopian tubes, omentum and lymph nodes Since the final diagnosis of primary could not be made it was considered as carcinoma of unkown primary

Q. Describe the Clinicopathologic Profile of Krukenberg Tumours

KTs are metastatic malignant OTs characterised by mucin-rich signet-ring adenocarcinoma [1]. In approximately 70% of the cases, gastric cancer (GC) is the primary malignancy, whilst gastric and colorectal (CRC) cancers collectively account for almost 90% of the primary site for these tumours [1]. Other less common primary sites described in the literature are breast, appendix, small intestine, gallbladder, urinary bladder, biliary tract, pancreas, ampulla of Vater, or uterine cervix [1]. The average age of diagnosis is 45 years, yet it can be diagnosed in all age groups. KTs are usually bilateral (60–70%) and can be asymptomatic or may manifest with non-specific GI signs and symptoms like abdominal or pelvic pain, bloating, ascites, or dyspareunia [14]. Occasionally, they might become autonomous and produce hormones causing vaginal bleeding, menstrual cycle irregularities, hirsutism, or rarely virilisation. Ascites is present in 50% of the cases and usually contains malignant cells [14].

KTs consist of both epithelial and stromal component. The epithelial component is composed of mucin-laden signet ring cells with eccentric hyperchromatic nuclei. The cytoplasm of the signet ring cells can be eosinophilic and granular, pale and vacuolated, or it can have a targetoid (bull's eye) appearance containing a large vacuole with a central to paracentral eosinophilic body composed of a droplet of mucin. Some tumour cells may lack mucin vacuole. Mitotic activity is sparse. The signet ring cells can be single, clustered, nested, or they can be arranged in tubules, acini, trabeculae, or cords. Several different patterns can appear in one tumour. The mesenchymal component of KTs is of ovarian stromal origin and is composed of plump and spindle-shaped cells with minimal cytologic atypia or mitotic activity. Stromal oedema or desmoplastic reaction can also be present focally [1]. ICH plays a key role in the diagnosis of KTs. CK7 and CK20 are the most commonly used antigens in ovarian neoplasms. Generally, a CK7+/CK20− immunophenotype is more typical of a primary ovarian carcinoma, whilst CK7-/CK20+ or CK7+/CK20+ immunoprofile is an indicator of KT from the GI tract [15]. Moreover, KTs of colorectal origin usually present positive staining for CEA and CDX2, which can guide the diagnosis further [15]. In this clinical scenario, the CK7+/CK20+ immunophenotype rendered the diagnosis challenging, and in the absence of clinical or radiological findings that could facilitate the diagnosis, the KT was characterised as of unknown primary origin.

Q. Role of Surgery in Krukenberg Tumours and Further Management

In this case, the patient underwent a complete cytoreductive surgery (CRS) for a provisionally suspected tubo-ovarian carcinoma. The intraoperative frozen section was inconclusive (malignant adenocarcinoma) and could not direct the diagnosis further. According to the pathological and IHC findings, the tumour was found to be metastatic; yet, the primary origin could not be identified. Often, the primary tumour is too small to be detected. In such a situation, diagnosis of a KT requires thorough radiographic (including USS and/or MRI breast) and endoscopic GI exploration (upper and lower GI endoscopy unremarkable) in an attempt to detect the primary carcinoma. Referral to colorectal and upper GI multidisciplinary team (MDT) meeting is also warranted to guide further management.

KTs of colorectal or gastric origin are an overall indicator of poor prognosis [4, 16]. Although the role of metastasectomy in metastatic colorectal and gastric cancer is established conferring symptom control and significant survival benefit [4, 17–20], the role of cytoreductive surgery in presence of disseminated distribution of primary cancer is questionable and removal of krukenberg tumours is with a palliative intent and also to confirm and exclude synchronous ovarian primary. Nonetheless, there is increasing evidence, mainly arising from small case series, that in absence of distant metastases, complete CRS with intraoperative chemotherapy, still does confer a survival benefit in highly selected patients [21–27]. To this end, R0 surgical resection without gross residual disease may improve prognosis in women with KTs [25–28].

In this case, owing to the lack of pre-operative diagnosis and inconclusive frozen section, heated intraperitoneal chemotherapy (HIPEC) with mitomycin was not administered. A recent study demonstrated encouraging results from the use of HIPEC [29]. Due to the peritoneal dissemination, post-operative chemotherapy is warranted. For colorectal and gastric cancers, metastasectomy in addition to chemotherapy was also found to improve survival compared to palliative chemotherapy alone, especially in cases of high-grade histology [30, 31]. Of note, ovarian metastases have been shown to be less responsive to chemotherapy compared to extra-ovarian sites [30, 31]. Therefore, surgical resection of these 'metastatic sanctuaries' even in the palliative setting is recommended, as they would often progress and result in symptoms during chemotherapy [30, 31]. Capecitabine and oxaliplatin (CAPOX), folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or 5-FU, leucovorin and irinotecan (FOLFIRI) with or without bevacizumab is the most commonly used combined chemotherapy [1, 14, 19–31]. Nonetheless, in the absence of definite diagnosis the choice of optimal chemotherapy regimen is rather challenging. According to ESMO guidelines, low-toxicity empirical chemotherapy is recommended for KT of unknown origin [32].

Q. Prognosis

The survival of patients with KT is influenced by the primary tumour site. Women with tumours originating in the breast exhibit the longest survival (median OS 31 months) followed by those with CRC (median OS 19–29 months), whilst the prognosis of women with a gastric cancer is the poorest (median OS 9–19 months), respectively [1, 14]. The absence of extra-ovarian peritoneal or visceral metastases, ascites, retro-peritoneal lymphadenopathy and the performance of metastasectomy are seemingly key factors for improving survival in women with KTs of any primary origin [1, 14]. The poor prognosis of metastatic gastric cancer is related to the fact that gastric cancers inherently carry a worse prognosis when compared to colorectal cancers. Women with KT of gastric origin usually exhibit a poor performance and nutritional status [1, 14]. Moreover, breast cancer is generally associated with a better prognosis compared with tumours of the GI tract [1, 14, 33].

KTs of unknown primary site have generally a poor prognosis; notwithstanding, there is a subgroup of women with more favourable survival. These subgroups are strictly defined, and, among others, include KTs of unknown primary site with a colorectal IHC or gene expression profiling and single metastatic deposits [32].

Case Scenario 3

Age, Parity, PS	50 years, P2+0, ECOG 0, BMI -25
Clinical presentation	Abdominal distension × 2 years (progressively increasing) Pain abdomen × 4 months Menopause 3 years' back Examination: Firm to hard mas measuring 12 weeks size uterus with restricted mobility, nodularity in pouch of Douglas more on right side, small mass 4 cm on left side mobile rectal mucosa free History of modified radical mastectomy done for invasive ductal carcinoma 5 years back. ER +, PR–ve, Her2 neu –ve. On letrozole 5 mg OD. Had received neoadjuvant chemotherapy (docetaxel + Epirubicin) for 6 cycles prior to surgery
Co morbidities	Hypertensive on amlodipine
CECT chest + abdomen + pelvis	Minimally enhancing large abdominopelvic predominantly cystic mass 7.9 × 13.1 × 10.5 cm with hyperdense solid areas within and multiple calcific foci along the wall of the lesion. Bilateral ovaries not visualized separately from the mass. Subcentimetric aortocaval and mesenteric nodes present. Pleural effusion present
Pleural fluid cytology	Positive for malignancy
Other investigations	CA125: 110 U/ml, CA19-9: 2 U/ml, CEA: 8.3 ng/ml, CA72-4: 1.02 U/ml, CA 15.3110 U/ml Hb: 12.3gm%, LFT/ KFT: Normal Upper GI endoscopy: Erosive gastritis Lower GI endoscopy: Normal

Case Scenario 4

Age, PS	49 years, P2+0, ECOG −1
Presenting complaints	Abdominal distension × 3 months Examination: 30 weeks size mass arising from pelvis Past history of sigmoid cancer, anterior resection T4N1M0 followed by chemotherapy and radiotherapy
Co morbidities	Nil
Ultrasound abdomen and pelvis	Solid cystic mass arising from left ovary 20 × 25 cm, uterus and contralateral ovary normal
Tumor markers	CEA: 300 **ng/mL**, CA125: 40

Questions for Case 3 and 4 Combined

Q. Confirmation of Diagnosis. What is the Role of Image Guided Biopsy?

In both cases, owing to the previous diagnosis and treatment of malignancy—BC and CRC, respectively - the likelihood of KT is rather high. Appropriate referral to the relevant MDT (breast, colorectal) is warranted. A thorough radiographic exploration is required to ascertain the extent of the disease. The histological confirmation is a key factor in guiding further management. This can be achieved by image guided biopsy, if possible (e.g. enlarged retro-peritoneal lymph nodes) or adnexectomy.

Q. Discuss Management Options: Role of Surgical Excision, Its Usefulness and Impact on Disease Prognosis, Further Management

In both cases, should a KT be diagnosed, metastatectomy can be offered following a thorough consultation of the patient on the implications and complications of the procedure, as it is seemingly associated with improved symptom control and survival [4, 17–22, 33]. Following surgical excision and histological confirmation, the decision as to the optimal adjuvant treatment, relies upon the relevant MDT.

In clinical scenario 3, the patient received adjuvant hormonal therapy (HT) with ovarian suppression and letrozole, as she was pre-menopausal at the time of the initial diagnosis. In the choice of second-line treatment, previous treatments, comorbidities, side effects, and also the expectations and wishes of the patient must all be taken into account [34]. Since hormone-receptor (HR) and *HER2* expression can change in the course of metastasization, determination of HR status should routinely be performed when relapse occurs [35]. Second-line HT with or without trastuzumab is the treatment of choice in case of HR+ status [36]. The choice of HT in postmenopausal women with metastatic BC depends upon the type and duration of previous therapy [34]. After upfront treatment with non-steroidal aromatase inhibitors (letrozole, anastrozole), the steroidal aromatase inhibitors and fulvestrant appear to be of equal value [37]. In case of *HER2*+ expression, a combination treatment with trastuzumab should be given, as it is associated with improved remission rate and the progression-free interval [38]. In case of HR negative tumour, chemotherapy is the treatment of choice [34]. For women with *HER2*negative, docetaxel or paclitaxel with or without addition of bevacizumab is the treatment of choice [34, 39]. Finally, for women with *HER2*+ status, trastuzumab in combination with docetaxel or paclitaxel is the treatment of choice [34, 39].

In clinical scenario 4, the patient was treated with anterior resection and chemoradiotherapy. As discussed above, KTs are characterised by marked chemoresistance, and metastatectomy prior to chemotherapy is seemingly associated with improved oncological outcomes [4, 17–22, 33]. Second line chemotherapy FOLFOX) FOLFIRI, or CAPOX) with or without addition of bevacizumab is required [4, 17–22, 33].

Q. How to Differentiate Between Metachronous Ovarian Tumour and Metastatic Ovarian Mass? What is the Difference in the Prognosis?

Tumour markers can guide the initial diagnosis. The markedly increased CA15-3 in clinical scenario 3 and CEA in clinical scenario 4, raised strong suspicion for recurrent breast cancer and CRC, respectively. However, pathological and IHC analysis represent the gold standard tests to differentiate between metachronous OT of either primary ovarian or metastatic origin. Metachronous tumour of primary ovarian origin is usually characterised by a CK7+/CK20—

immunophenotype vis-a-vis metachronous KT of colorectal origin, which is usually characterised by a CK7−/CK20+ immunoprofile [1, 15]. Moreover, CDX2 and CEA immunoreactivity increases the confidence in diagnosing the colorectal origin of the tumour [1, 15]. In case of metachronous KT of breast origin, CK7, GCDFP-15 and ER positive staining is the most commonly observed IHC profile, whilst CK20, vimentin or CEA positivity may also be seen in a few occasions [40]. When the immunophenotype is vague, *PTEN* staining may play a role in differentiating between primary and metastatic ovarian tumour, as diffuse *PTEN* staining supports the likelihood of primary ovarian carcinoma [41]. The prognosis of metachronous ovarian carcinoma is significantly better vis-a-vismetachronous KT of either colorectal or breast origin, which is relatively poor [1, 14, 33].

Q. Is Genetic Testing Required and Discuss Their Implications?

BRCA1 and *BRCA2* genes produce proteins related to repair of damaged DNA. *BRCA 1/2* gene mutations are associated with higher risk for both BC and ovarian cancer [41]. *BRCA1/2* testing is required for genetic counselling purposes [41]. Furthermore, women with *BRCA* mutations and/or homologous recombination deficiency (HRD) are eligible candidates for maintenance treatment with (poly (ADP)-ribose polymerase) inhibitors (PARP-i) in case of primary ovarian cancer diagnosis [42]. Finally, women with *BRCA* mutations and metastatic BC appear to have poorer prognosis [4, 33].

Lynch syndrome is an autosomal dominant disorder which is related to germline mutations in DNA mismatch repair (*MMR*) genes, which confer higher risk for colorectal, endometrial, ovarian, bladder, kidney and other types of cancer [43]. The features of Lynch syndrome-related ovarian cancer are: 1. young onset (<50 years), 2. early-stage (approximately 50% FIGO stage I), 3. usually serous type histology, 4. high attribution of *MSH6* deficiency [43]. Similarly to *BRCA* mutations, appropriate genetic counselling is required [43]. Diagnosis of Lynch syndrome plays an important role in tailoring adjuvant treatment. Irinotecan hydrochloride (CPT-11) has favourable effects on *MMR*-deficient tumours with high microsatellite instability, and in such cases, CPT-based bevacizumab with FOLFIRI, FOLFOX or CAPOX is the treatment of choice [44]. *KRAS* gene should also be tested, and patients with *KRAS* mutations should be excluded from cetuximab/panitumumab administration [44].

Key Points

- Krukenberg tumour is a rare metastatic signet ring cell ovarian tumour, accounting for 1–2% of all ovarian tumours.
- The stomach is the primary site in the majority of Krukenbergtumours followed by colorectal, appendiceal and breast carcinomas.
- Immunohistochemistry plays a cardinal role in differentiating between primary and metastatic ovarian tumours.
- Women with tumours originating in the breast exhibit the longer survival followed by those with colorectal cancer, while whilst the prognosis of women with gastric cancer the poorest.
- For colorectal and gastric cancer, metastatectomy in addition to chemotherapy was also found to improve survival compared to palliative chemotherapy alone. For highly selected cases, three might be a role of cytoreductive surgery. The role of hyperthermic intraperitoneal chemotherapy remains debatable.
- In women with breast cancer, metastatectomy appears to prolong survival and improve quality of life.
- Genetic testing is crucial for counselling and tailoring management.

References

1. Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med. 2006;130:1725–30.
2. Novak C, Gray LA. Krukenberg tumor of the ovary: clinical and pathological study of four cases. Surg Gynecol Obstet. 1938;66:157–65.

3. Serov SF, Scully RE. Histological typing of ovarian tumors. International Histological Classification of Tumours. 9:(Geneva). WHO. 1973.
4. Wu F, Zhao X, Mi B, Feng LU, Yuan NA, Lei F, Li M, Zhao X. Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol Clin Oncol. 2015;3(6):1323–8.
5. Abiko K, Baba T, Ogawa M, et al. Minimal deviation mucinous adenocarcinoma ('adenoma malignum') of the uterine corpus. Pathol Int. 2010;60(1):42–7.
6. Frumovitz M, Schmeler KM, Malpica A, Sood AK, Gershenson DM. Unmasking the complexities of mucinous ovarian carcinoma. Gynecol Oncol. 2010;117(3):491–6.
7. Nishio S, Mikami Y, Tokunaga H, Yaegashi N, Satoh T, Saito M, Okamoto A, et al. Analysis of gastric-type mucinous carcinoma of the uterine cervix - an aggressive tumor with a poor prognosis: a multi-institutional study. Gynecol Oncol. 2019;153(1):13–9.
8. Liu S, Guo Y, Li B, Zhang H, Zhang R, Zheng S. Analysis of Clinicopathological features of cervical mucinous adenocarcinoma with a solitary ovarian metastatic mass as the first manifestation. Cancer Manag Res. 2020;12:8965–73.
9. Nagel CI, Thomas SK, Richardson DL, Kehoe SM, Miller DS, Lea JS. Adnexal masses requiring surgical intervention in women with advanced cervical cancer. Gynecol Oncol. 2014;134(3):552–5.
10. Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol. 2006;101(2):234–7.
11. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol. 2003;27(7):985–93.
12. Stolnicu S, Barsan I, Hoang L, et al. Diagnostic algorithmic proposal based on comprehensive immunohistochemical evaluation of 297 invasive endocervical adenocarcinomas. Am J Surg Pathol. 2018;42(8):989–1000.
13. Sakuragi N. A multivariate analysis of blood vessel and lymph vessel invasion as predictors of ovarian and lymph node metastases in patients with cervical carcinoma. Cancer. 2000;88(11):2578–83.
14. Kubeček O, Laco J, Špaček J, Petera J, Kopecký J, Kubečková A, Filip S. The pathogenesis, diagnosis, and management of metastatic tumors to the ovary: a comprehensive review. Clin Exp Metastasis. 2017;34(5):295–307.
15. Park SY, Kim HS, Hong EK, Kim WH. Expression of cytokeratins 7 and 20 in primary carcinomas of the stomach and colorectum and their value in the differential diagnosis of metastatic carcinomas to the ovary. Hum Pathol. 2002;33(11):1078–85.
16. Tan KL, Tan WS, Lim JF, Eu KW. Krukenberg tumors of colorectal origin: a dismal outcome--experience of a tertiary center. Int J Color Dis. 2010;25(2):233–8.
17. Rayson D, Bouttell E, Whiston F, Stitt L. Outcome after ovarian/adnexal metastectomy in metastatic colorectal carcinoma. J Surg Oncol. 2000;75:186–92.
18. Morrow M, Enker WE. Late ovarian metastases in carcinoma of the colon and rectum. Arch Surg. 1984;119:1385–8.
19. Seow-En I, Hwarng G, Tan GHC, Ho LML, Teo MCC. Palliative surgery for Krukenberg tumors - 12-year experience and review of the literature. World J Clin Oncol. 2018;9(1):13–9.
20. Jiang R, Tang J, Cheng X, Zang RY. Surgical treatment for patients with different origins of Krukenberg tumors: outcomes and prognostic factors. Eur J Surg Oncol. 2009;35:92–7.
21. Ayhan A, Guvenal T, Salman MC, Ozyuncu O, Sakinci M, Basaran M. The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. Gynecol Oncol. 2005;98:235–41.
22. Kim WY, Kim TJ, Kim SE, Lee JW, Lee JH, Kim BG, Bae DS. The role of cytoreductive surgery for nongenital tract metastatic tumors to the ovaries. Eur J Obstet Gynecol Reprod Biol. 2010;149:97–101.
23. Kim KH, Lee KW, Baek SK, Chang HJ, Kim YJ, Park J, Kim JH, Kim HH, Lee JS. Survival benefit of gastrectomy ± metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. Gastric Cancer. 2011;14:130–8.
24. Elias D, Goere D, Di Pietrantonio D, Boige V, Malka D, Kohneh-Shahri N, Dromain C, Ducreux M. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2008;247:445–50.
25. Yu P, Huang L, Cheng G, Yang L, Dai G, Ying J, Du Y. Treatment strategy and prognostic factors for Krukenberg tumors of gastric origin: report of a 10-year single-center experience from China. Oncotarget. 2017;8(47):82558–70.
26. Feng Q, Pei W, Zheng ZX, Bi JJ, Yuan XH. Clinicopathologic characteristics and prognostic factors of 63 gastric cancer patients with metachronous ovarian metastasis. Cancer Biol Med. 2013;10:86–91.
27. Jun SY, Park JK. Metachronous ovarian metastases following resection of the primary gastric cancer. J Gastric Cancer. 2011;11:31–7.
28. McCormick CC, Giuntoli RL 2nd, Gardner GJ, Schulick RD, Judson K, Ronnett BM, et al. The role of cytoreductive surgery for colon cancer metastatic to the ovary. Gynecol Oncol. 2007;105(3):791–5.
29. Rosa F, Marrelli D, Morgagni P, Cipollari C, Vittimberga G, Framarini M, Cozzaglio L, et al. Krukenberg tumors of gastric origin: the rationale of surgical resection and perioperative treatments in a multicenter western experience. World J Surg. 2016;40:921–8.
30. Cho JH, Lim JY, Choi AR, Choi SM, Kim JW, Choi SH, Cho JY. Comparison of surgery plus chemotherapy and palliative chemotherapy alone for advanced

gastric cancer with Krukenberg tumor. Cancer Res Treat. 2015;47:697–705.
31. Goéré D, Daveau C, Elias D, Boige V, Tomasic G, Bonnet S, Pocard M, Dromain C, Ducreux M, Lasser P, et al. The differential response to chemotherapy of ovarian metastases from colorectal carcinoma. Eur J Surg Oncol. 2008;34:1335–9.
32. Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G, et al. Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v133–8.
33. Bacalbasa N, Balescu I, Vilcu I, Halmaciu I, Diaconu CC, Dima S, Brezean I. Krukenberg tumors from breast cancer-literature review. Arch Balkan Med Union. 2020;55(2):320–3.
34. Gerber B, Freund M, Reimer T. Recurrent breast cancer: treatment strategies for maintaining and prolonging good quality of life. Dtsch Arztebl Int. 2010;107(6):85–91.
35. Broom RJ, Tang PA, Simmons C, et al. Changes in estrogen receptor, progesterone receptor and her-2/neu status with time: discordance rates between primary and metastatic breast cancer. Anticancer Res. 2009;29:1557–62.
36. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer. Results from the randomized phase III TAnDEM study. J Clin Oncol. 2009;27:5529–37.
37. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 2008;26:1664–70.
38. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
39. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol. 2005;23:5542–51.
40. Lagendijk JH, Mullink H, van Diest PJ, Meijer GA, Meijer CJ. Immunohistochemical differentiation between primary adenocarcinomas of the ovary and ovarian metastases of colonic and breast origin. Comparison between a statistical and an intuitive approach. J Clin Pathol. 1999;52(4):283–90.
41. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, Senkus E, ESMO Guidelines Committee. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016;27(suppl 5):v103–10.
42. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, Pignata S. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59.
43. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, Church JM, et al. US Multi-Society Task Force on Colorectal Cancer. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2014;147(2):502–26.
44. Yamamoto S, Nagashima K, Kawakami T, Mitani S, Komoda M, Tsuji Y, Izawa N, et al. Second-line chemotherapy after early disease progression during first-line chemotherapy containing bevacizumab for patients with metastatic colorectal cancer. BMC Cancer. 2021;21(1):1159.

8 Malignant Ovarian Germ Cell Tumours

Tejumola Olaoye

Introduction

Malignant ovarian germ cell tumours (MOGCT) are rare neoplasms of the ovary accounting for less than 5% of all malignant tumors of the ovary in western populations [1, 2]. Nevertheless, MOGCT represent up to 15% of malignant ovarian masses in black and asian populations [3]. This group of disorders predominantly affects young women most commonly less than 30 years old [4]. Despite the preponderance in adolescents and young women, MOGCT can affect women of any age including postmenopausal women. MOGCT originate from the primordial germ cells of the ovary; the tumor types are divided into dysgerminoma and non dysgerminoma types. Dysgerminomas are the most common sub-type of MOGCT; the tumour type is the biological equivalent to seminomas in males. Non dysgerminoma tumours include yolk sac tumours (YST) otherwise known as endodermal sinus tumours; immature teratoma; embryonal tumours, choriocarcinoma and mixed cell types. MOGCT tend to characteristically present as a large unilateral solid ovarian mass in young women [5]. MOGCTs tend to present at an early stage due to their inherently symptomatic nature. Due to their rapid growth symptoms associated with the mass pressure effect are often present. Women often present with acute abdominal pain as a result of intra-tumoral hemorrhage and torsion. The overall prognosis when diagnosed early is excellent and due to early stage presentation and chemosensitive nature of the tumours. MOGCTs are rapidly progressive tumours with a propensity to metastasize quickly, therefore expeditious diagnosis and treatment is the cornerstone of their management [3].

In this chapter we will review cases of MOGCT, their management and prognosis.

Case 1: Dysgerminoma

Age, PS	28 years, P0 + 1, ECOG −0
Presenting complaints	Lump abdomen × 6 months Amenorrhea × 3 months preceded by history of heavy menstrual bleeding
Co morbidities	Nil
Ultrasound abdomen and pelvis	Uterus normal size, empty, right adnexal mass 15 × 18 cm with solid areas and increased vascularity
CECT abdomen and pelvis	Right adnexal mass 18 × 20 × 16 cm with marked contrast enhancement and solid areas. Left ovary and uterus are normal. No retroperitoneal lymph nodes. Rest of the abdomen normal.

T. Olaoye (✉)
Pan-Birmingham Gynaecological Cancer Centre, Sandwell and West Birmingham NHS Trust, Birmingham, UK
e-mail: tejumola.olaoye@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_8

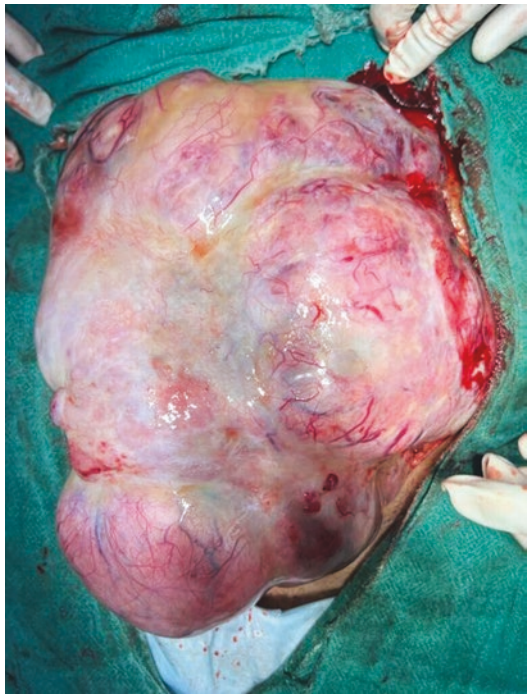


Fig. 8.1 Gross appearance of dysgerminoma appearing as lobulated, solid, soft fleshy tumors with cream color appearance

Tumor markers	LDH 850 IU/L, BHCG 2455 IU/ml, CA125: 25 U/ml, AFP2 ng/ml
Surgery	Staging laparotomy-cytology + right salpingo oophorectomy + infracolic omentectomy (Fig. 8.1)
Histology	HPE: Dysgerminoma, peritoneal cytology positive, omentum negative FIGO stage 1C3

Q. Salient Clinical and Histopathological Features of Dysgerminoma

Dysgerminoma's represent 0.9–2% of all malignant ovarian tumors and 33–37% of all MOGCT [6]. Due to the biological similarity between dysgerminomas in females and seminomas in males, treatment paradigms of dysgerminomas have been largely directed by the paradigms used for its male counterpart [1]. The peak incidence for dysgerminoma's is at 10 to 30 years old with 90% of tumors being diagnosed in women under the age of 30; dysgerminoma represent 10% of all cancers in women under the age of 20 years old [6].Dysgerminoma's may be associated with dysgenetic gonads in 5–10% of cases like Swyer syndrome (46 XY karyotype), mixed gonadal dysgenesis (45X/46XX) or partial gonadal dysgenesis (46XX). Consideration of prophylactic oophorectomy in these patients is appropriate [3]. Histologically, there may be pure dysgerminomas and these tend to have a good prognosis however 15% of dysgerminomas will have a mixed type with the variable admixture of other germinal elements including teratoma, embryonic carcinoma or yolk sac tumour (YST). Tumor spread is by direct invasion with lymphatic and hematogenous spread occurring much less frequently [3].

Dysgerminomas generally present in the archetypal way of all MOGCT; as a large unilateral solid mass often measuring as large as 15 cm. 10% to 15% of all pure dysgerminomas present as bilateral ovarian masses [1]. Due to the rapid growing nature of the tumour, patients present with increased abdominal girth, distension/bloating, and pain. Occasionally, they may present with acute abdominal pain as a result of ovarian torsion or intratumoral hemorrhage.

Dysgerminoma contain syncytiotrophoblastic giant cells which secrete lactate dehydrogenase (LDH) consequently, LDH is the most appropriate tumour marker. Ultrasound shows a large solid tumour with smooth contour and heterogeneous echogenicity and marked vascularisation [7].

Grossly, dysgerminoma appear as lobulated, soft, fleshy, and gray-white or light tan. Upon microscopy dysgerminomas are morphologically described as undifferentiated germ cells and large vesicular cells dispersed in sheets or cords interspersed by scant fibrous stroma, with variable degree of atypia. Mature lymphocytes and occasional granulomas infiltrate the fibrous stroma. Immunohistochemistry makers include CD117, OCT3, and OCT4 [6].

Q. What Are the Factors Which Are Likely to Influence Management? Discuss Role of Lymphadenectomy and Fertility Preserving Surgery

Initial treatment should be expedited and treatment modalities are determined by suspected disease distribution. Other important factors are age, desire for fertility preservation and clinical presentation.

If the tumour is confined to the ovary without capsule rupture or positive ascitic cytology (FIGO stage 1A) then surgery alone is adequate treatment [3]. In cases of disease more advanced that FIGO stage 1A, as seen in the present case, surgery followed by adjuvant chemotherapy is recommended.

Due to the symptomatic nature of the tumour the majority of cases present in stage one as confined to the ovary. However formal surgical staging with fertility sparing surgery, often unilateral salpingo oophorectomy, should be undertaken. Surgical staging should also include peritoneal biopsies and omental biopsy or infracolic omentectomy. Systematic lymphadenectomy has not been shown to improve outcomes therefore is not advocated and only resection of bulky lymph nodes is required [5]. Even in cases of advanced disease, fertility sparing surgical paradigms can be pursued if the contralateral ovary fallopian tube and uterus appear normal. It is rare that this disease presents with advanced metastatic spread however in those cases strong consideration towards neoadjuvant chemotherapy should be given [2, 5]. When planning surgical resection aiming for complete cytoreduction may not always be in the patient's best interest. Due to the rapid tumour doubling time disease recurrence can occur within weeks following surgical resection, therefore a large cytoreductive procedure requiring a prolonged recovery time may worsen outcomes. In those circumstances resection of large tumor masses alone to allow quick recovery and timely administration of adjuvant chemotherapy is preferable [3, 5].

Q. Further Management, Indications of Chemotherapy, Regimes and Potential Complications

In FIGO stage 1A dysgerminoma surgery alone is appropriate. All other stages of disease cisplatin-based chemotherapy should be offered. The standard regime Bleomycin, Etoposide and Cisplatin is offered for four cycles. This regimen can be safely used in most women with an awareness regarding the adverse effects profile including myelosuppression and pulmonary fibrosis [5]. Due to the rapidly growing nature of this tumour, any reduction in chemotherapy dose intensity may lead to poor outcomes; therefore if bone marrow suppression occurs growth factors are given in conjunction with the chemotherapeutic regimen [7]. Early stage dysgerminomas have a good prognosis with up to 100% 5 year overall survival (OS) with advanced disease having a poorer prognosis with 63% 5 year OS [4, 8].

Q. Follow Up

Follow up is advised every three monthly for the first 2 years following diagnosis. Each visit requires a good history, physical examination, tumor marker estimation. Imaging depends on clinician's discretion depending on symptoms, if there is a rise in tumor marker levels, or examination reveals any abnormality [7, 8]. Ultrasound pelvis should be done 6 monthly in women who have undergone fertility preservation [5].Women are advised to avoid conception within the first 2 years of diagnosis as majority of recurrences occur within this time frame, with 75% occurring within the first 12 month [4]. The risk of recurrence has been variably reported being between 18–52% of cases [4]. In cases of residual disease following chemotherapy or recurrent disease salvage surgery should be considered.

Q. Management of Bilateral Ovarian Dysgerminoma

In the uncommon circumstance of bilateral ovarian dysgerminoma fertility sparing surgery may be considered if this is what the patient wishes. In these cases, preservation off the healthy ovarian tissue in the least affected ovary may be attempted. For example, oophorectomy of the most severely affected ovary and cystectomy of the contralateral ovary [5, 6]. This paradigm may be pursued as there is no evidence that removing uninvolved ovary improved survival even in advanced disease.

Case 2: Yolk Sac Tumor

Age, PS	26 years, nulliparous, ECOG −0
Clinical presentation	Lump abdomen and abdominal pain Large mass arising from pelvis corresponding to 30 weeks uterine size
Co morbidities	Nil
Tumor markers	CA-125:18 U/ml, HCG:2 IU/ml, LDH:162 IU/L, AFP: 600 ng/ml
CECT chest + abdomen + pelvis	Mass most likely arising from left ovary with solid cystic areas, omental cake with nodules 2 cm, uterus, right ovary normal
Surgery	Staging laparotomy: Peritoneal cytology + left salpingo oophorectomy + removal of gross peritoneal deposits (2–3 cm) + infracolic omentectomy Intraoperative findings are shown in Fig. 8.2
Histology	Yolk sac tumor, peritoneal implants >2 cm positive for malignancy, omentum deposits largest size 2.5 cm positive for malignancy 3C yolk sac tumor

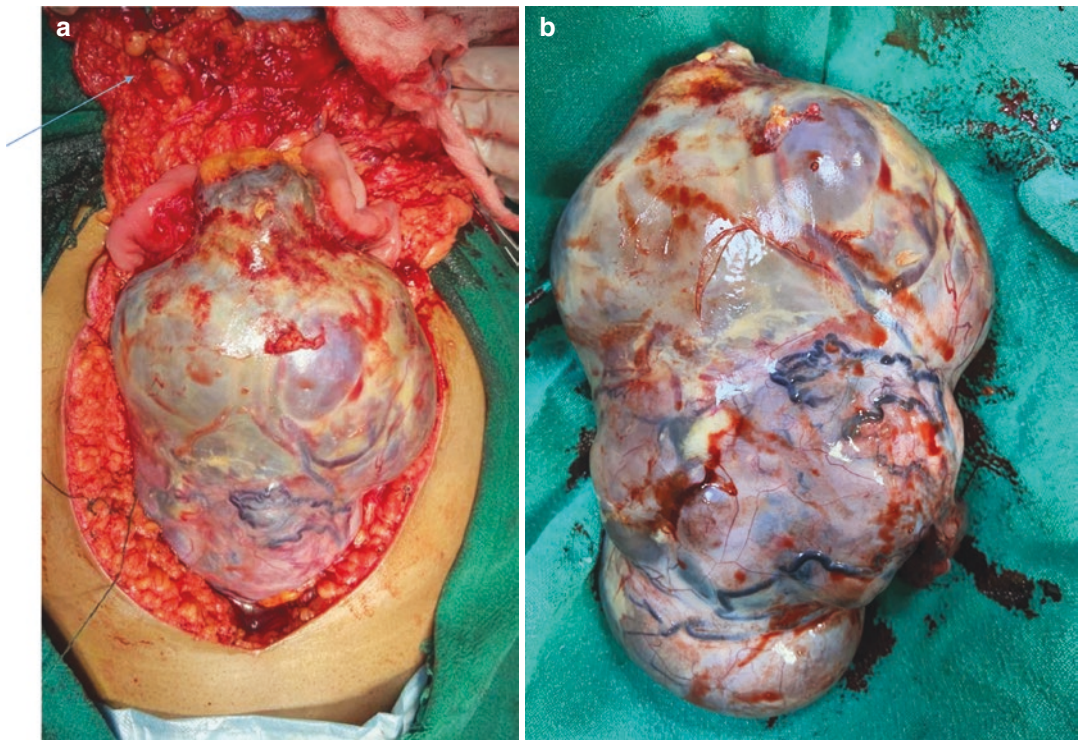


Fig. 8.2 (**a**) Midline laparotomy done for malignant germ cell tumor (yolk sac tumor), a large ovarian mass occupying the whole of abdomen, arrow indicated nodules in omentum. (**b**) Intact ovarian tumor with increased surface vascularity

Q. Work Up and Investigations

Ovarian yolk sac tumours (YST) are very rare malignancies of the ovary, with an incident rate of 0.048/100,000 women years. YST tend to present in the characteristic mechanism of all MOGCT; a unilateral large solid ovarian tumour with associated abdominal enlargement and pain. Primary investigation with tumours markers including CA125, AFP, LDH and HCG is necessary and YST are associated with elevated AFP levels. As with all solid ovarian masses in young women adequate characterization with imaging is fundamental. At ultrasound the appearance of YST is usually unilateral large and well encapsulated. It will have a mixture of solid and cystic components and may show areas of haemorrhage or necrosis. On cross sectional imaging there may be a "wet honeycomb" appearance. Imaging of the chest should be undertaken to rule out spread of disease. A contrast enhanced CT of chest abdomen and pelvis is advised to assess tumor spread.

Q. Further Management

As with all MOGCT, treatment includes expeditious surgical management with adequate staging. Although the primary aim of surgery is to ensure complete macroscopic clearance, however pursuing maximal effort cytoreductive surgery may not always be appropriate. YST are extremely chemosensitive whilst also being rapidly progressive. Ensuring that chemotherapy can be commenced in a timely fashion is of the utmost importance and any surgical effort should prioritise this consideration. Fertility sparing surgery should be pursued where the contralateral ovary and uterus appear normal.

The recommended adjuvant chemotherapy regimen is BEP. Although current paradigms of YST management indicate all tumours irrespective of stage receive BEP chemotherapy, De la Motte Rouge et al. was able to demonstrate that FIGO stage 1A disease had no recurrence with a median follow-up of 85 months after only surgical management [9].Modern paradigms are giving some consideration to active surveillance in FIGO 1A YST, however this is not yet broadly accepted practice and will require further investigation to assess suitability.

Q. Prognosis

YST are highly malignant and considered to have the worst prognosis amongst all of the MOGCTs. The average mortality in YST versus dysgerminoma is 13% and 5.3% respectively [10]. Disease spread tends to be intra-peritoneal with invasion of local structures and metastasis within the peritoneal cavity. Retroperitoneal lymph node involvement tends to occur at a later stage when intraperitoneal metastasis is already apparent. YST can either be pure tumours or mixed tumours [10]. It has been demonstrated that the prognosis of both pure YST and mixed YST showed no significant difference in overall survival (OS) indicating yolk sac component to be the driver of prognosis in mixed tumors [10]. Satoh et al. established that mixed YST with more than 50% yolk sac component showed no significant difference in preoperative AFP level compared to pure YST. Conversely mixed YST with less than 50% yolk sac component had a significantly lower preoperative AFP level compared to pure yolk sac tumors. Interestingly the same study demonstrated a prognostic implication of AFP with levels greater than 33,000 being significantly associated with poorer overall prognosis [10].

As with all ovarian tumors prognosis is significantly determined by stage at diagnosis. The estimated 5 year overall survival for women with stage one disease was 92–94% reducing to 44.5% in stage four disease. BEP compared to non BEP chemotherapeutic regimes had a 5 year overall survival of 93.6% versus 74.6% P = 0.0004 [10]. This difference was most pronounced in stage III/IV disease with BEP versus PVB 5 year OS of 94% versus 66.7% respectively. Age at diagnosis was also identified as a poor prognostic indicator with women diagnosed above age 22 having worse OS and progression

free survival [9, 10]. AFP level at diagnosis was also prognostic which higher levels being associated with poorer outcomes [9]. Normalization of AFP following surgery was also shown to be prognostic; De la Motte Rouge et al. established that AFP serum halving times of greater than 10 days was associated with a poorer prognosis. Recurrent disease in yolk sac tumors has a poor prognosis and despite salvage treatment complete remission was only achieved in 28% of these patients [9].

Q. Follow Up

As with dysgerminomas, very close monitoring is undertaken in these patients. Follow up is with regular serological markers, clinical review and imaging. Women are advised to avoid conception within the first 2 years of diagnosis asked the majority of recurrences occur within this time frame [5, 9].

Q. Patient Wants Conception. What Should Be the Further Plan of Management? Is Completion Surgery Required After Completion of Child Bearing?

There has been no evidence demonstrating any detriment to prognosis associated with fertility sparing surgery, in fact De la Motte Rouge et al. demonstrated that fertility sparing surgery actually showed a prognostic benefit [9].Satoh et al. we're able to prove the safety of BEP chemotherapeutic regime with regards to ongoing fertility. Their data showed 97% of women who received BEP recovered menstruation within 24 months and 70% of women who were nulliparous pretreatment went on to conceive and have successful pregnancies [10]. Completion surgery is usually not recommended after completion of child bearing.

Case 3: Immature Teratoma with Growing Teratoma Syndrome

Age, PS	16 years ECOG = 0
Presenting complaints	Known case of immature teratoma stage 3 with peritoneal implants (intraoperative finding Fig. 8.3) Received BEP X 4 cycles 5 years isolated recurrence in rectosigmoid: Resection and anastomosis done: Mature teratoma 3 years later liver recurrence. Underwent partial liver resection: Mature teratoma At present recurrence in pouch of Douglas- 10 cm mass
Co morbidities	Nil
CECT abdomen + pelvis	Large complex solid cystic mass 12 × 10 cm in pouch of Douglas
Tumor markers	CA-125:13, HCG:24, AFP:5, LDH:120

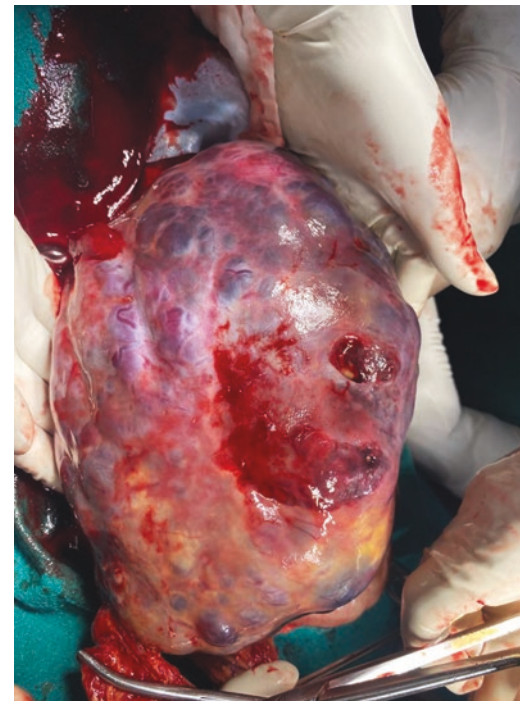


Fig. 8.3 Gross appearance Immature teratoma: large mass with bosselations and with increased surface vascularity

Q. What Is Growing Teratoma Syndrome and Its Management?

Immature teratomas (IMT) are rare ovarian germ cell tumors, account for approximately 1% of ovarian malignancies, and approximately one third of malignant germ cell tumors [8, 11]. They are differentiated from mature teratoma tumors by the presence of immature neuroepithelial cells. IMT have no specific tumour marker profile with variable expression of raised AFP and CA 125. As with the other types of MOGCT they tend to be unilateral and large presenting as an abdominal mass with pain [8].Unlike all other forms of MOGCT IMT are graded; this assessment is made according to immature neuroepithelial content. Grade one tumors often have abundant mature teratomas content intermixed with small amounts of immature neuroepithelial cells conversely grade three tumours may have very little or completely absent mature tissues. Grading of these tumours is of significance due to its prognostic value when managing the condition. IMT are treated with surgical resection and surgical management should aim for fertility sparing approach due to the highly chemo sensitive nature of this tumor in young girls. IMT maybe associated with mature teratoma in the contralateral ovary; In in these circumstances ovarian cystectomy alone should be performed so as not to sacrifice the fertility ambitions of the patient [11]. Adjuvant chemotherapy (BEP) is indicated in all stages except stage 1Agrade 1 tumours in which active surveillance can be an option [5].

Growing teratoma syndrome (GTS) is a rare complication of IMT. It is characterized by an increase in metastatic tumour mass after complete eradication of the primary malignant ovarian germ cell tumour with normal tumor markers [12]. These metastatic deposits are non-invasive and therefore non-malignant. These tumors can have a rapid expansion rate ranging from 0.5 to 1 cm per month. The behavior of this tumour type is unpredictable due to its aggressive local spread and the potential for malignant change to incurable malignant disease. These tumors can appear at variable time frames after commencing or completing chemotherapy with a median time frame of 18 to 27 months [13]. Tumors masses associated with GTS are often found within the peritoneal cavity or the retroperitoneum. The mechanism for the development of GTS has not yet been elucidated; there are two postulated theories regarding its development. Firstly, that the cytotoxic chemotherapy induces differentiation of malignant cells into benign teratomous elements. The second theory is that chemotherapy can only destroy malignant cell types leaving behind the benign teratomous elements [12, 13].

GTS should be suspected in patients who have an enlarging tumour with normalizing tumor markers during chemotherapy. GTS is resistant to chemo and radiotherapy and management relies solely on maximal surgical effort to excise all of the tumours [12]. GTS have a high recurrence rate when incompletely excised (72–83%) as opposed to those which are completely excised (0–4%) [12, 13]. Gliomatosis peritonei (GP) Is the implantation of mature glial tissues within the peritoneal cavity, often affecting the omentum [14]. Although a non-malignant process in itself GP is an adverse prognostic factor and is associated with recurrent GTS. Other risk factors for the development of GTS include higher histological grade of tumour, higher stage at diagnosis and incomplete resection of the primary tumor.

Q. Fertility Options and Outcomes in These Patients

The presence of GTS should not mandate fertility sacrificing surgery as there is no additional benefit in reducing recurrence or progression. If the uterus and contralateral ovary appear normal, they may remain in situ to allow the patient to fulfill fertility aspirations [12, 13].

Q. Discuss Holistic Care for Young Cancer Survivors

MOGCT typically affect very young women or adolescent girls. Prior to the diagnosis the majority of these patients will not have had any significant healthcare issue or had to make any considerations of their own mortality, receiving the diagnosis will change that dramatically. The diagnosis added to the potential challenges faced by young women transitioning from adolescence to adulthood can also add an additional dimension of distress to this experience [10]. The impact of now adopting the "sick" role, the uncertainty regarding outcomes, feelings regarding body image and wishes for future fertility may present a complex emotional landscape for these patients to navigate. Sensitively and openly addressing these issues with patients is crucial [10]. Identifying area of specific concerns and working collaboratively with the patient to address them is vital. As the long-term prognosis of MOGCT is very good, the survivorship of this group of patients is likely to be long. Therefore, focusing on quality-of-life issues should be a cornerstone of the holistic management of these patients.

Key Points

1. MGOCT are rare tumours that primarily affect adolescent girls and young women
2. MGOCT tend to be symptomatic due to large abdomino-pelvic mass and associated pain
3. These tumours grow rapidly and can spread quickly therefore rapid treatment is vital
4. All ovarian masses associated with solid elements should be assessed as potential MOGCT with imaging of abdomen/pelvis, tumour markers (AFP, LDH, HCG, CA125) and chest imaging.
5. Surgical management should be fertility sparing where a normal uterus, fallopian tube and contralateral ovary are present
6. The tumours are exquisitely chemosensitive and generally will be treated with adjuvant BEP chemotherapy regime for 3–4 cycles.
7. Long term survival outcomes are excellent, quality of life implications of treatment and support should always be considered.

References

1. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):347–55.
2. Uccello M, Boussios S, Samartzis EP, Moschetta M. Systemic anti-cancer treatment in malignant ovarian germ cell tumours (MOGCTs): current management and promising approaches. Ann Transl Med. 2020;8(24):1713.
3. Tîrnovanu MC, Florea ID, Tănase A, et al. Uncommon metastasis of ovarian dysgerminoma: a case report and review of the literature. Medicina (Kaunas). 2021;57(6):534.
4. Cheung A, Shah S, Parker J, Soor P, Limbu A, Sheriff M, Boussios S. Non-epithelial ovarian cancers: how much do we really know? Int J Environ Res Public Health. 2022;19(3):1106.
5. Ray-Coquard I, Morice P, Lorusso D, Prat J, Oaknin A, Pautier P, Colombo N, ESMO Guidelines Committee. Non-epithelial ovarian cancer: ESMO clinical practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv1–iv18.
6. Ajao M, Vachon T, Snyder P. Ovarian dysgerminoma: a case report and literature review. Mil Med. 2013;178(8):e954–5.
7. Zhang XW, Zhai LR, Huang DW, Jiang ZD, Yu T, Liu SY, Cui MH. Pregnancy with giant ovarian dysgerminoma: a case report and literature review. Medicine (Baltimore). 2020;99(41):e21214.
8. Devaja O, Papadopoulos A. Current management of immature teratoma of the ovary. Arch Oncol. 2000;8(3):127–9.
9. de La Motte Rouge T, Pautier P, Rey A, Duvillard P, Kerbrat P, Troalen F, Morice P, Haie-Meder C, Culine S, Lhommé C. Prognostic factors in women treated for ovarian yolk sac tumour: a retrospective analysis of 84 cases. Eur J Cancer. 2011;47(2):175–82.
10. Satoh T, Aoki Y, Kasamatsu T, et al. Administration of standard-dose BEP regimen (bleomycin+etoposide+cisplatin) is essential for treatment of ovarian yolk sac tumour. Eur J Cancer. 2015;51(3):340–51.
11. Wang D, Cang W, Zhu S, Jia C, Cao D, Yang J, Xiang Y. Oncological and reproductive outcomes in patients with advanced-stage ovarian immature teratoma: experience from a tertiary center. Front Oncol. 2022;12:822341.
12. Li S, Liu Z, Dong C, Long F, Liu Q, Sun D, Gao Z, Wang L. Growing teratoma syndrome secondary to

ovarian giant immature teratoma in an adolescent girl: a case report and literature review. Medicine (Baltimore). 2016;95(7):e2647.
13. Wang D, Zhu S, Jia C, Cao D, Wu M, Shen K, Yang J, Pan L, Cheng N, Xiang Y. Diagnosis and management of growing teratoma syndrome after ovarian immature teratoma: a single center experience. Gynecol Oncol. 2020;157(1):94–100.
14. Wang D, Jia CW, Feng RE, Shi HH, Sun J. Gliomatosisperitonei: a series of eight cases and review of the literature. J Ovarian Res. 2016;9(1):45.

9 Stromal Tumours of Ovary: Granulosa Cell Tumours, Leydig Cell Tumours, Thecoma

Tejumola Olaoye and Kavita Singh

Introduction

Ovarian cancers are the leading cause of death from gynecological malignancy worldwide. Despite their commonality of origin within the female gonad, ovarian cancers are a heterogeneous group arising from varying cell lines of the organ. 90% of ovarian cancers are epithelial in origin with the remaining arising from non-epithelial tissues; sex cord stromal cells and germ cells [1, 2].

Sex Cord Stromal Tumours (SCST) arise from the primitive sex cord and or stromal cells of the gonad; namely the Granulosa, Theca, Sertoli and Leydig cells, they represent 8% of all ovarian malignancies [3–6]. These tumors tend to affect younger women, most commonly in their middle age however they also affect younger populations of women including prepubescent and adolescent girls. Granulosa cell tumours (GCT) are the most frequently diagnosed SCST representing 70–90% of all SCSTs [7, 8]. The global incidence rate for SCSTs stands at 3 per 100,000, however this is increasing by 2.3% annually [8]. Risk factors for the development of SCST have been identified and include a BMI greater than 30 kg/m^2 and the family history of breast cancer. Similarly, the use of the oral contraceptive pill and parity have been identified as protective factors against the development of SCST [4].

All SCST tend to present in a uniform manner, as a large unilateral mass with secondary endocrine manifestations of the disease. Granulosa cell tumours (GCT) accounts for 90% of SCST and 5% of all malignant ovarian tumors. Granulosa cell tumours are endocrinologically active causing symptoms associated with hyperestrogenism. Two histological subtypes of GCT have been identified, adult and juvenile. Adult GCT (AGCT) represents 95% of the disease burden with juvenile GCT (JGCT) representing 5% [7, 9, 10]. Despite their macroscopic morphological similarities, significant microscopic and molecular variations exist. This fundamental difference between the two disease types manifests in differing clinical presentations [6]. Sertoli-Leydig cell tumours (SLCT) are a rarer tumour type accounting for less than 1% of all ovarian malignancies. These tumours may also be endocrinologically active; however, their effects tend to be as a result of a hyperandrogenic state.

T. Olaoye (✉)
Gynaecological Oncology, Pan Birmingham Gynaecological Cancer Centre, Birmingham, UK
e-mail: tejumola.olaoye@nhs.net

K. Singh
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_9

Case 1: Juvenile Granulosa Cell Tumor

Age, PS	13 years ECOG −0
Presenting complaints	Puberty menorrhagia with lump abdomen × 2 months
Co morbidities	Anemia (Hb-7 gm%)
Ultrasound abdomen and pelvis	Uterus normal size, empty, left complex adnexal mass 10 × 12 cm Fig. 9.1
MRI abdomen + pelvis	Left complex solid cystic solid mass 10 × 12 cm, left iliac nodes 1 × 1 cm Moderate ascites Right ovary and uterus normal Upper abdomen normal
Tumor markers	LDH 1150 U/L, BHCG:1.20 U/ml, AFP 0.47 U/ml, CA125: 240 KU/L Inhibin: >1050 pg/ml
Surgery	Staging laparotomy with left salpingo-oophorectomy with omental, peritoneal biopsies and removal of left external iliac node Intraoperative findings: 350 ml of ascitic fluid Left ovarian mass 10 × 10 cm, smooth surface, intact capsule with solid, cystic and haemorrhagic areas on cut section Left external iliac node enlarged Upper abdomen + omentum normal
Histology	Frozen section: Suggestive of malignant ovarian neoplasm possibly granulosa cell tumor Histology: Juvenile Granulosa cell tumor 1C3; cytology positive Omentum, left external iliac node, peritoneal biopsy negative for any metastatic disease

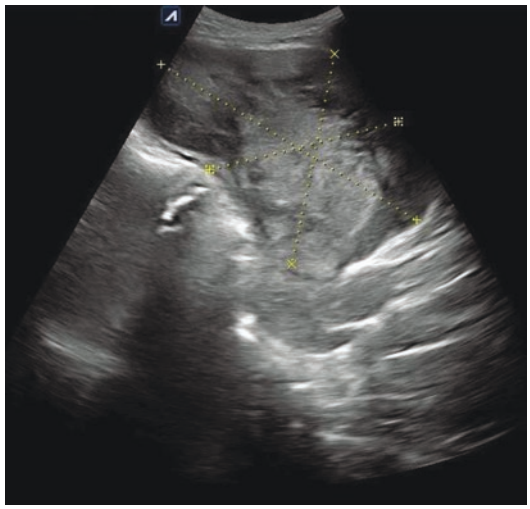


Fig. 9.1 Left complex adnexal mass 10 × 12 cm

Q. Discuss Diagnostic Work Up and Management of This Case

JGCT are a rare ovarian tumour representing only 5% of all granulosa cell tumours. These malignant neoplasms are most frequently identified in young women and girls. Although they can affect all age groups, 97% of tumours are diagnosed in females within the first three decades of life [11] with more than 40% being diagnosed in girls less than 10 years old [12, 13]. JGCT account for 12% of ovarian neoplasms in the pediatric/adolescent population; representing 67% of SCST in that age group [13]. JGCT often present as a unilateral abdominal mass with associated pain. Juvenile GCT are associated with ovarian torsion [14, 15] and acute abdomen with haemoperitoneum in 6% of cases [11]. As a hormonally active tumour it may also manifest with symptoms of excess estrogen. In pre-pubertal girls' precocious puberty (breast bud development, pubic hair, vaginal bleeding, advanced bone age) and abnormal uterine bleeding (menorrhagia or intermenstrual bleeding) in post pubertal females [12–14]. Despite this, 30% of JGCT's do not produce estradiol due to the lack of theca cells in the tumor stroma [11] therefore the absence of estrogenic symptoms does not rule out the disorder. Serum CA125 is not an ideal tumour marker, and is only elevated in approximately 40% of cases, however, Inhibin B and Anti-Mullerian Hormone (AMH) have both been demonstrated to be reliable tumor markers [11]. JGCTs are unilateral masses with irregular septa in the vast majority of cases. Grossly they appear indistinct from AGCT radiologically and at macroscopic assessment they tend to be large

with average tumour sizes of 10–15 cm [11, 13]. At imaging they appear solid or mainly solid with cystic areas in the majority, with a cystic appearance alone representing only 30% of the disease [16]. Ultrasonographically, they appear spongiform with the solid portion being heterogenous in appearance [14]. On MRI scan JGCT have distinctive features; a sponge like appearance with solid areas of intermediate isointense signal density with multiple cystic spaces on T2 weighted MRI images. Haemorrhagic foci of high signal intensity on T1 weighted may also be identified [14, 16]. Synchronous endometrial thickening may also be noted as a result of the hyper-estrogenic effect of the tumour.

Q. Distinguishing Features of Juvenile GCT from Adult GCT

Although JGCT may appear similar to AGCT macroscopically but microscopically and molecularly there are significant differences. JGCT can only be accurately differentiated from AGCT by histopathological assessment. Unlike AGCT, FOXL2 mutations are rarely found in JGCT and do not seem to play a role in the development of this disease [1]. Somatic AKT1 mutations appear to be the driving molecular abnormality associated with the development JGCT. More than 60% of JGCT have AKT1 in tandem duplications leading to activation of mutated AKT1 oncoprotein [1, 4]. At microscopy the classical Call-Exner bodies, nuclear grooves, and coffee bean nuclei of a AGCT are not present [13, 16]. JGCT are characterized by diffusely arranged tumor cells formed as sheets or nodules with varying percentage of follicular and cystic structures [11, 13]. In JGCT are often found to have eosinophilic cytoplasm with immature nuclei with nuclear atypia are noted. There is increased mitotic activity demonstrated by mitotic figures numbers ranging from 5–37 per 10 high power fields [13, 16]. Due to their mitotically active nature there is often increased nuclear to cytoplasmic ratio [13]. Inhibin and calretinin have been found to be the two most useful immunohistochemical markers for diagnosing JGCT [11].

Q. What Is the Impact of Surgical Treatment of JGCT on Fertility

Over 90% of JGCT are stage 1 at diagnosis [13, 14] with up to 95% of patients being stage1 in some series [11]. Contralateral ovarian involvement and lymph node involvement is rare therefore systematic lymphadenectomy and biopsy of the contralateral ovary appears to hold no benefit therefore is not recommended [11]. A minority of patients will present with advanced (stage II–IV) disease; these cases tend to have an aggressive clinical course with overall poor clinical outcomes [13]. Stage 1A/B tumours have a good overall prognosis. In their case series, Schultz et al. (2017), demonstrated no recurrences or deaths in all stage 1A/B patients treated with surgery alone with a median follow up of 9 months (1–77 months). Ndhlovu et al. (2021) showed no deaths in any patient diagnosed with stage 1A disease with a median follow up of 35 months. This data supports the view that patients with stage 1 A/B tumours with favorable histological features can be treated with surgery alone [11, 12]. For women with stage 1 disease, the long-term outcomes of those treated with radical surgery versus fertility sparing surgery do not differ significantly therefore management with fertility sparing surgery like unilateral salpingo-oophorectomy is appropriate in young women and girls if future fertility is desired [11, 14] (Fig. 9.2).

Q. What Is the Role of Adjuvant Treatment in JGCT?

FIGO stage at the time of diagnosis is the most important prognostic factor for JGTC. There are other unfavorable features which influence adjuvant treatment including high mitotic index, and incomplete surgery (macroscopic residual disease) [11]. Schultz et al. (2017) found 27% of patients diagnosed with stage 1C or greater died of their disease at a median follow up of 17 months (10–44) [12]. In their series, Ndhlovu et al. (2021) recorded only one

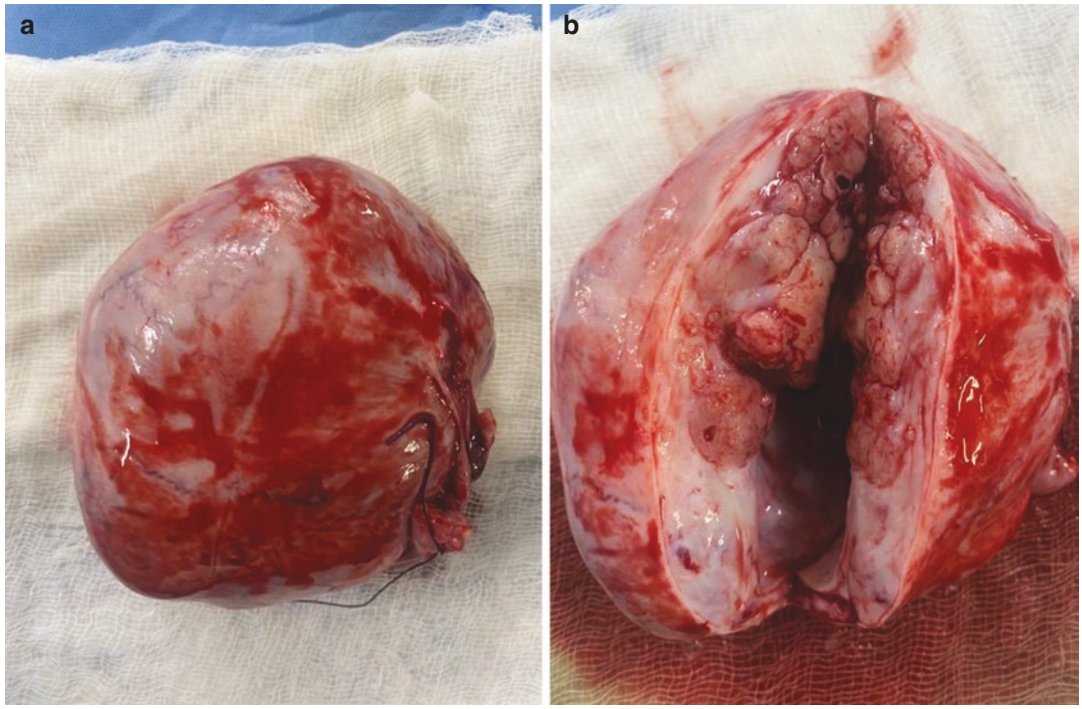


Fig. 9.2 (**a**) Left ovarian mass 10 × 10 cm, smooth surface, intact capsule. (**b**) Solid, cystic & haemorrhagic areas on cut section

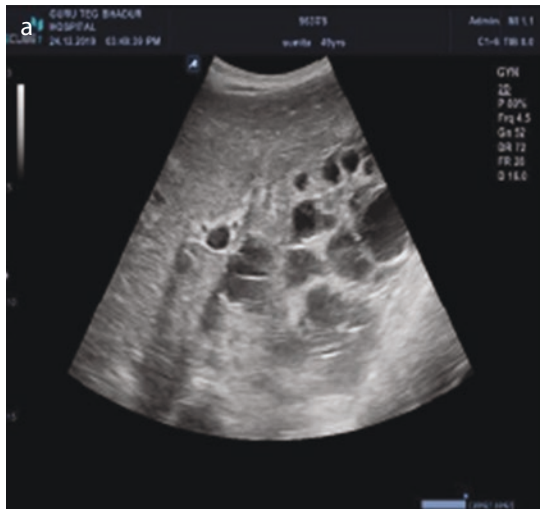
recurrence and death, this was of a patient initially diagnosed with stage 1C disease; this patient recurred 8 months after initial treatment and died 32 months after initial diagnosis [11]. Due to rarity of the condition, there is a paucity of data regarding the optimal adjuvant chemotherapy regime. Currently the most frequently used is bleomycin, etoposide and cisplatin (BEP), however carboplatin and paclitaxel are also sometimes used. There is very little evidence available regarding the value of postoperative chemotherapy in prepubertal stage 1C patients. It has been demonstrated that all patients who experienced recurrence of JGCT with mitotically active primary tumors (greater than 20 mitoses per high power fields) subsequently died [13]. Currently both ESMO and NCCN recommend adjuvant chemotherapy in stage 2–4 disease and consideration of chemotherapy in stage 1C disease, this is most significant in high-risk disease (high mitotic index, nuclear atypia or extracapsular disease [13] In addition, anti-angiogenic therapy and radiotherapy have been used to improve outcomes of advanced JGCT [11].

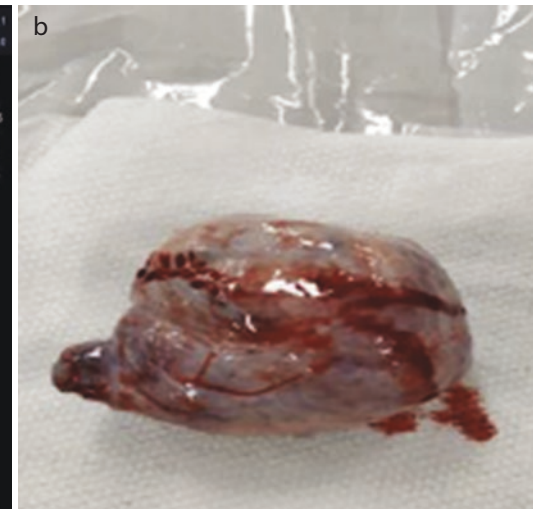
Q. Future Prognosis and Follow Up of JGCT

Outcome of JGCT is unpredictable and is dependent upon the stage at presentation, histologically high risk factors and type of surgery performed. Long term survival has been noted in some advanced stage disease with the paradigm of achieving complete cytoreduction and adjuvant chemotherapy. JGCT often have a rapid clinical course with the majority of recurrences occurring within the first 3 years of diagnosis [11]. Therefore, usefulness of long term follow-up of JGCT is not well established unlike that of AGCT. Currently both ESMO and NCCN recommend the standard ovarian cancer follow up regimens for this tumour type. Due to the rare nature of this tumour widespread knowledge and expertise in its management is not available.

Case 2: Adult Granulosa Cell Tumor

Age, PS	48 years, P4L3 ECOG −02
Presenting complaints	Heavy menstrual bleeding 8 months Examination: Uterus 10 weeks size, right adnexal mass 10 × 12 cm restricted
Co morbidities	Hypothyroidism, fever with splenomegaly, thrombocytopenia, anemia, bilateral poly cystic kidney
Ultrasound abdomen and pelvis	Uterus bulky, endometrial thickness: 18 mm Right ovary 10 cm solid cystic mass with areas s/o hemorrhage (Fig. 9.3a)
Endometrial biopsy	Endometrial hyperplasia without atypia
Tumor markers	CA125: 75.3, CA19.9: 228.3, CEA: 1.64 Inhibin B: 877.9 ku/l
Endometrial biopsy	Hyperplasia without atypia
CECT abdomen + pelvis	Right complex ovarian mass 12 × 13 cm, ascites+ Uterus normal, no retroperitoneal nodes Upper abdomen normal
Surgery	Staging laparotomy- Total abdominal hysterectomy+ bilateral salpingo oophorectomy+ infracolic omentectomy Outcome R0 (Fig. 9.3b, c)
Histology	Right ovary: Adult granulosa cell tumor, Calretinin +ve, inhibin B +ve Omental deposits +ve, largest tumor size 1 cm Uterus normal, hyperplasia without atypia, left tube and ovary normal Stage IIIB





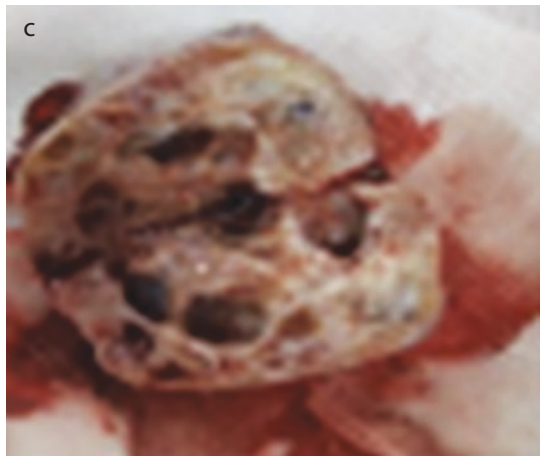


Fig. 9.3 (**a**) Gray scale ultrasound image shows multiloculated solid and cystic mass. (**b**) Gross image shows specimen- encapsulated with smooth lobulated surface. (**c**) Cut section shows multiloculated solid cystic areas with few necrotic areas

Q. What Is the Pathogenesis of Adult Granulosa Cell Tumour?

Granulosa cells form part of the cellular stroma that surrounds the ovarian follicle and supports the developing oocyte. The physiological function of granulosa cell is to produce oestradiol by converting androstenedione and testosterone to oestradiol via aromatase following stimulation by follicle stimulating hormone (FSH). Estrogen binds to granulosa cell estrogen receptors which subsequently activate cell signaling pathways which inhibit granulosa cell apoptosis [4]. The granulosa cell also to produces AMH, inhibin A and Inhibin B which support the developing oocyte. Usually, granulosa cells proliferate in response to rising circulating FSH and LH; in normal circumstances excess estradiol suppresses GnRH and consequently suppresses FSH and LH [13]. AGCT exhibits a molecular profile which is consistent with the typical granulosa cells of a normal ovary [10, 17]. Advances in molecular analysis enabled the identification the single point missense mutation in the FOXL2 gene by Shah et al. (2009) FOXL2: C134W. This mutation is present in 97% of all AGCT and is now considered pathognomonic for the disease [4, 17]. FOXL2 has diverse transcriptional activities including cell proliferation, cell death and tumorigenesis [17]. FOXL2 is known to form a complex with steroidogenic factor 1 (SF-1); SF-1 is a regulator of aromatase function in granulosa cells. It has been postulated that FOXL2:C134W directly targets aromatase function through its interaction with SF-1 leading to increased estrogen production [18].

AGCT is an indolent tumor that often presents in an early stage thus it is generally associated with a good prognosis. Nevertheless, AGCT is associated with late recurrence, up to 40 years after initial presentation, therefore requires lifelong follow up [10].

Q. Discuss Salient Presentation Findings in GCT

AGCT represent 2–5% of all ovarian malignancies; being 70–90% of all SCST [7, 19]. AGCT arises as a result of a pathogenic point mutation FOXL2 [8]. AGCT tend to present in perimenopausal and early postmenopausal women with a median age 50–54 [10, 20]. Despite its preponderance for diagnosis in the fifth decade of life, AGCT can be diagnosed in women of all ages and rarely may be diagnosed in pre-adolescent girls [10]. AGCT demonstrate an age specific increase in incidence rates that drops off at the age of the menopause. Interestingly there is a higher incidence of breast carcinoma in women diagnosed with AGCT [15].

The tumour arises from the hormonally active granulosa cell; a somatic cell component of the ovarian follicle, which produces estradiol inhibin and AMH [20]. The tumours are unilateral and large with the median size of 12 cm at presentation [9]. Women often present with abdominal distension and pain [12] due to their vascular nature, emergency presentation with acute haemoperitoneum is frequent accounting for 10% of cases [9, 10]. Over 60% of AGCT are hormonally active presenting with manifestations of excess estrogen. Hyper-estrogenic symptoms are dependent upon the hormonal receptor status of the tumour. Pre-menopausal women present with AGCT may present with abnormal uterine bleeding (menorrhagia or intermenstrual bleeding); postmenopausal women often present with postmenopausal bleeding; prepubertal girls may present with precocious puberty (development of pubic hair, breasts, early menarche) [9, 10]. Endometrial hyperplasia is found 25–50% of cases with endometrial cancer being present in 5–11% [4, 7].

CA125 serum tumour marker is often within the normal range [17, 21], however AMH and Inhibin are elevated at presentation [4]. Both AMH and Inhibin correlate with tumour size and drop immediately after surgical resection of the tumour [4, 7]. Upon imaging AGCT appear as a unilateral mass, with heterogenous mostly solid and solid-cystic appearances. The tumor is highly vascularised with a haemorrhagic components [9, 22]. Macroscopically AGCT resemble JGCT, being a solid tumour with yellow tan coloured tissue and areas of necrosis. Microscopically distinctive diagnostic features are present; Call-Exner bodies (gland like structures resembling ovarian follicles) and coffee bean nuclei (grooved

pale and round nuclei displaying a low mitotic rate) are classical features of AGCT [16].

Due to their indolent nature, AGCT are most effectively treated with surgical resection. Standard staging procedures with midline laparotomy, hysterectomy, bilateral salpingo-oophorectomy omental biopsy/omentectomy should be performed. If the tumour is confined to the ovary with no evidence of intra-abdominal spill (stage 1A) then fertility sparing surgery may be offered [1]. If fertility sparing surgery is undertaken, endometrial biopsy should be performed concurrently to ensure any endometrial pathology is appropriately identified and treated [5]. Lymph node metastasis is rare occurring in 3% of cases, most often in advanced stage disease [4, 13]. Routine systematic lymphadenectomy has been shown to be of no benefit therefore should not be undertaken [13].

Q. Risks of Recurrence and Overall Prognosis

The majority of AGCT presents as early-stage disease, with 78–91% presenting as stage 1 [1, 9, 10]. Due to the indolent nature of AGCT and its early presentation the overall prognosis is exceedingly good with a 100% three-year survival in stage 1 [15]. The overall five-year survival for stage 1 disease 90–98%; stage 2 60–84%; stage 3 61%; and stage 4 13–41% [4, 6, 22]. With an overall 10-year survival for stage 1.84–95%; stage 2 50–65%; 1 stage 3 and 4 17–33% [7, 19]. The median overall survival varies greatly with median overall survival for stage I/II of 180 months and median overall survival for stage III&IV of 58-month [6]. Up to 80% of those with advanced AGCT or recurrent tumours will die of their disease [2].

The indolent slowly progressive nature of these tumours predisposes these patients to late recurrences and cases have been reported of as late as 40 years after initial surgery [7, 10]. Twenty percent of those diagnosed with stage 1 disease and 43–48% with stage II/III/IV disease relapse within 20 years of initial surgery [4]. Nearly half, 47%, of relapses, occur more than 5 years after initial diagnosis [15]. Stage at diagnosis is the most important prognostic factor [10, 22]. The median recurrence free survival in stage 1A/B is 159 months; in stage 1C 62 months; in stage II to IV is 35 months [15]. The median overall survival was reduced in patients with recurrent disease compared to patients with no relapse 26.5 versus 30.6 years [4]. Although stage at diagnosis is the most significant prognostic indicator several other patient and tumour characteristics have been identified to have prognostic implications. Tumour rupture specifically impacts overall survival; Dridi et al. demonstrated a differential in 25-year survival between stage 1A and 1C with survival rates of 86% and 60% respectively [5]. Aberrant tumour p53, a mitotic index of greater than 4/10 mitoses per high power field, and diabetes have all been associated with poor prognosis and increased risk of recurrence [4, 5, 23]. A protective impact of increasing parity and use of oral contraceptive pills have also been identified [22].

Surgical treatment is the mainstay of treatment of all types of GCT. Adjuvant treatment with chemotherapy and hormonal therapies are aimed at slowing progression. The single most important predictor of tumour recurrence is therefore surgical outcome and the presence of residual disease. Maximal surgical effort should be expended to aim for complete cytoreduction (R0), this is equally important whether at primary or recurrence surgery [19, 21]. Residual disease whether R1 or R2 increases the risk of tumour recurrence [23]; optimal cytoreduction (R1) the overall five-year survival is 82% with a median overall recurrence free survival of 60 months and if macroscopic residual disease is present (R2) the overall 5-year survival is 22% with median overall recurrence free survival of 19 months [5]. Surgical treatment for true stage 1A disease maybe curative if operated without any spillage and will do well even with less conservative fertility sparing surgery. Dridi et al. (2018) demonstrated that women with stage 1A disease who underwent fertility sparing surgery had an excellent 10-year survival of 94%. When comparing the outcomes of stage 1A who had radical versus fertility sparing surgery Dridi et al. (2018) were able to show no significant difference in overall five-year survival with 98% vs 97% respectively [5].

Q. Further Management and Need for Adjuvant Treatment

AGCT are indolent tumours of low malignant potential consequently they remain relatively insensitive to chemotherapy [23]. Evidence demonstrating the benefit of chemotherapy in AGCT is equivocal. Adjuvant chemotherapy has not been shown to improve the recurrence free survival in stage 1 disease [6, 15]. Nasioudis et al. (2019) found no statistic benefit in the treatment of stage 1C disease when treatment with observation and adjuvant chemotherapy were compared; 5-year survival of 50% and 27% respectively (p = 0.4) [24]. Chemotherapy did not influence overall survival but does influence recurrence free interval in higher stage disease (stage II to IV) [13]. Mangili et al. (2013) showed the median recurrence free survival was 53.2 months, and demonstrated a positive influence adjuvant chemotherapy on recurrence free interval with the median recurrence free survival of 72.5 months in patients who received chemotherapy and of 48 months in the group who received no adjuvant chemotherapy in higher stage disease. Influence of chemotherapy on overall survival was not demonstrated in this study.

The pelvis is the most common site of recurrence, though recurrences can appear in any part of the abdomen, liver and retroperitoneum, chest [25, 26]. ESMO guidelines recommend active surveillance in all stages >1C1 and adjuvant chemotherapy for all > stage 1C2 [6]

Different chemotherapy regimens have been used for GCT. Platinum based chemotherapy is usually used for post-operative adjuvant chemotherapy. The most common regimen is Bleomycin. Etoposide, Cisplatin (BEP). Six cycles of BEP has been shown to reduce the risk of relapse in high risk patients [14]. Taxanes with platinum have been shown to have similar activity against AGCT as BEP with less associated toxicity, consequently the use of Carboplatin and Paclitaxel is becoming more frequent [27]. Antiangiogenic treatments have also been shown to have activity against AGCT [27].

When treating recurrent disease, a combined approach of both surgery and chemotherapy has been shown to be most effective. In the management of recurrence, surgery alone is associated with 10.6-fold increased risk of further recurrence compared to combined approach of treatment with surgery and chemotherapy. Chemotherapy alone is associated with 15-fold increased risk of second recurrence and 13.4-fold increased risk of death compared to combined treatment with surgery and chemotherapy [23].

Suppression of endogenous estrogen production has been shown to have benefit as a long-term treatment for AGCT. Hormonal treatments include aromatase inhibitors (anastrozole letrozole exemestane), GnRH agonists (goserelin, zoladex), progestogens, selective estrogen receptor modulators (SERM) (Tamoxifen). Hormonal treatment leads to an overall clinical benefit in 71–100% of patients [2, 19]. Fifty nine percent of patients with radiologically visible recurrence will have stable disease at 6 months if treated with anastrozole, with a clinical benefit rate of 80% at 12 weeks. A prospective randomised trial (PARAGON trial) showed clinical benefit with usage of aromatase inhibitors with recurrent and metastatic GCT but extent of benefit was less than what was demonstrated by previous case series [19].

Case 3: Inadvertent Diagnosis of Adult Granulosa Cell Tumor

Age, PS	45 years P2+0 ECOG –02
Presenting complaints	Heavy menstrual bleeding 8 months
Co morbidities	Anemia (Hb-7 gm%), diabetic on OHA (borderline control)
Ultrasound abdomen and pelvis	Uterus bulky, endometrial thickness: 18 mm Right ovary bulky, left ovary normal
Endometrial biopsy	Endometrial hyperplasia without atypia
Tumor markers	CA125: 52
Surgery	Total laparoscopic hysterectomy + bilateral salpingo oophorectomy
Histology	Uterus myohyperplasia and endometrial hyperplasia Right ovary shows 1 × 1 cm foci of adult granulosa cell tumor. Calretinin+ve, inhibin positive

Q. Discuss Further Management

Despite the overall excellent prognosis, the risk of tumour recurrence remains substantial at 20% in stage 1 disease. Both inhibin and AMH serum levels fall immediately following surgical resection of AGCT, however establishing a baseline at diagnosis is beneficial for ongoing monitoring.

Q. Adjuvant Treatment, Follow Up and Prognosis

Early stage AGCT have an excellent prognosis with 98% five- year survival. These are tumours of low malignant potential with limited response to cytotoxic chemotherapy. Stage 1A disease is managed by surgical treatment alone; outcomes are favorable with no role for adjuvant systemic therapy. Nonetheless 20% of stage 1 disease will recur within 20 years of diagnosis therefore ongoing follow up is required. CA125 is an unreliable tumour marker for AGCT. AMH and Inhibin are far more accurate serological tumour markers. An elevated inhibin may precede clinical symptoms of recurrence by a up to 2 years, with median duration of 11 months before clinically evident disease [5]. Long term follow-up with Inhibin or AMH tumour markers is necessary, however, this does not necessarily need to be within a hospital setting. Disease recurrence can occur decades after primary diagnosis, therefore lifelong follow up is best practice for these patients.

Case 4: Recurrent Granulosa Cell Tumor (Adult Type)

Age, PS	45 years P2+0 ECOG −02
Presenting complaints	Abdominal pain × 2 months H/o TAH + BSO done for left adnexal mass with heavy menstrual bleeding 8 years back; HPE: Adult granulosa cell tumor stage IA
Co morbidities	Hypertensive on amlodipine 5 md OD, h/o appendicectomy
CT scan (thorax + abdomen + pelvis)	4 × 5 cm heterogeous mass on left pelvic side wall encasing the left ureter, left hydronephrosis, left external iliac lymph nodes enlarged 1 × 2 cm upper abdomen, chest NAD
Tumor markers	Inhibin: 250 pg/ml, CA125: 428 U/mL

Q. Further Management and Prognosis?

AGCT is well known as a disease with a significant risk of recurrence however due to its indolent nature this may be many years or even decades after the initial diagnosis. Recurrence occurs in 20% of stage 1 disease and in greater than 40% of stage 2–4 disease. Inhibin and AMH are reliable tumour markers rising with recurrence in a proportional manner to tumour size [4].There is no role of image guided biopsy in presence of raised s inhibin levels unless the identified lesion is in unusual location and any other pathology is suspected. Image guided biopsy impacts outcome of localized recurrence in GCT. Conversely CA125 often remains within the normal range [21]. Patients often have multiple recurrences requiring repeated treatments [28].The recurrence free survival decreases in conjunction with an increase in aggressiveness of the disease with each subsequent recurrence [13]. Mangili et al. (2013) demonstrated a median time to first recurrence being 4–5 years with a subsequent median time to second recurrence of 37 months and a median time to third recurrence of 41 months [25, 26]. Fotopoulou et al. (2010) demonstrated a similar pattern with a median time to first recurrence of 38 months, a median time to second recurrence of 20 months, and a median time to third recurrence of 18 months [21].

Disease recurrence can be single site or multisite with the pelvis being the most common location. The location of recurrence does not influence

survival or prognosis nor does having multisite disease [23, 25, 26]. Achieving complete cytoreduction (R0) at surgical treatment of AGCT recurrence improves overall survival. If R0 is not achieved there is 3.5-fold increased risk of a subsequent recurrence. The median post recurrence free survival is 25 months with a median post recurrence overall survival of 90 months [23]. The prognosis following recurrence is unfavorable with an overall mortality of up to 60–80% [20]. However this mortality risk is over a prolong period with a three-year survival after first recurrence 82% and five-year survival after first recurrence 77% [23].

Hormonal therapies have been used in recurrent GCT to stabilize disease and slow down progression so as to allow greater time intervals between surgeries and secondly may also help to down stage disease to facilitate complete cytoreduction. Hormonal treatment can provide clinical benefit (complete response, partial response, or stable disease) in 70–100% of AGCT patients1 [8, 29] Van Meurs et al. (2015) demonstrated a 18% objective response rate (complete response or partial response) in patients taking hormonal treatments for recurrent AGCT. Stable disease was achieved in 64% of patients within that cohort. Banerjee et al. (2021) demonstrated of patients with clinically apparent (visible at imaging) recurrent disease commenced on anastrozole a median progression free survival of 8.6 months was identified. The longest progression free survival in that cohort was recorded at 53.5 months. Canario et al. found an objective response rate of 56% and the clinical benefit rate of 100% in patients treated with letrozole. Schwarts and Huang (2016) found letrozole to be more efficacious when managing AGCT recurrence than anastrozole, possibly due to greater hypoestrogenic effect of letrozole when compared to anastrozole [30]. Van Meurs demonstrated that although objective benefit of hormonal treatments may be present, it is not durable in the long-term with 75% maintaining objective benefit for 12 months or less. Interestingly, Banerjee et al. (2021) revealed patients with greater than 30% fall in inhibin at 3 months after commencing anastrozole had an appreciable benefit in progression free survival. Those who did not achieve a 30% or greater fall in inhibin at 3 months had no change in progression free survival [19]. These findings support benefit from hormonal treatments in delaying inevitable repeated surgeries while also acting as an adjuvant treatment following surgical resection of disease.

Case 5: Sertoli- Leydig Cell Tumor

Age, PS	25 years ECOG −0
Presenting complaints	Primary infertility × 2 years Oligomenorrhea (2 days/ 3–4 months) × 2 years Hirsutism × 6 months
Co morbidities	Nil
Ultrasound abdomen and pelvis	Uterus normal size, empty, right complex adnexal mass 8 × 9 cm
MRI abdomen + pelvis	Right complex solid cystic solid mass 10 × 12 cm, uterus and left adnexa normal, no retroperitoneal lymphadenopathy Upper abdomen normal
Tumor markers	LDH 100, BHCG:2, AFP: 3.2, CA125: 50
Surgery	Laparoscopy with right salpingo oophorectomy with omental and peritoneal biopsy (Fig. 9.4)
Histology	Moderately differentiated sertoli leydig cell tumor Omental and peritoneal biopsy negative

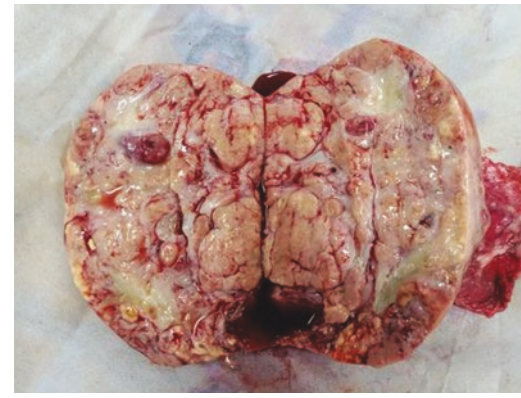


Fig. 9.4 Gross specimen showing lobulated, solid tumor with yellowish to brown in color

Q. Discuss Management

Sertoli Leydig Cell Tumours (SLCT) are a rare ovarian neoplasm accounting for 0.2–0.5% of all primary ovarian carcinomas [8, 27, 28]. SLCT most frequently present in young women often less than 25 years old, however they are not exclusive to that age group and may be diagnosed in women of all ages [8, 27, 31]. SLCT present with hormonal symptoms in approximately 50% of cases, the remaining will be hormonally inert and often identified following complaints of abdominal mass symptoms. These tumours may also be incidentally identified during investigations of infertility or amenorrhea [27]. The hormonal effects may be hyperandrogenic or more rarely hyper-estrogenic phenomena [28, 32].

Patients may typically present with symptoms of abdominal distension, pressure and pain. Those with endocrine manifestation will often present with typical symptoms of androgen excess including oligomenorrhea, amenorrhea, hirsutism and occasionally virilization. Less frequently symptoms of excess estrogen including dysfunctional uterine bleeding or post-menopausal bleeding may predominate [27, 28, 32]. As a result of this hyperestrogenic state, endometrial pathology may also be identified in women with SLCT. Akman et al. noted 7% of patients with SLCT were diagnosed with endometrial hyperplasia and 7% were diagnosed with endometrial cancer at presentation [8]. Pain is the most common presenting symptom in women diagnosed with SLCT, with 57% complaining of pain at diagnosis [8].

The most accurate serological marker indicating the neoplasm may be of SLCT origin is testosterone which is elevated in 67% of cases [28]. Serum CA125 is raised in 15–17% of cases [8, 28], serum alpha fetoprotein is raised in 20% of cases and CA 19-9 raised in 20% of cases. SLCT are unilateral in 98% of cases and range in size from one up to 35 cm with an average size of 15 cm with larger tumours being less likely to be endocrinologically active [8, 27, 28, 32]. At imaging SLCT appear as a purely solid mass or majority solid-cystic mass in approximately 60% of cases [28].

Q. What Are the Diagnostic Histological Features?

SLCT are characterized by the presence of testicular structures (sertoli and leydig cells). Despite their consistent presence these cells are not always hormonally active [28]. Upon macroscopic review the tumours appear as a solid mass with a smooth external surface which may be lobulated. Internally they are solid with a yellow or yellow tan appearance [8]. Histologically they are divided into well differentiated tumours, intermediately differentiated tumours, poorly differentiated tumours, tumours with heterologous elements and tumours with retiform patterns [8, 32]. The degree of differentiation, presence of heterologous elements and presence of retiform pattern are prognostic indicators for SLCT [8, 28].

SLCT maybe well, intermediate or poorly differentiated tumours, latter are difficult to distinguish from high grade sarcoma sometimes. Well differentiated tumours behave as benign with a uniform histological pattern and low mitotic count and are less common than intermediate and poorly differentiated SLCT [27, 28, 31]. Both intermediate and poorly differentiated SLCT show a high mitotic activity of 5/10 mitoses per high power field and 20/10 mitoses per high power field respectively [27]. Histologically, SLCT may contain heterologous components in 11–50%, however, these findings are rarely encountered in well differentiated tumours [8, 28] Heterologous elements may include carcinoid tumor, endodermal elements, mesenchymal elements (e.g. immature skeletal muscle or cartilage) [8]. The retiform variant of SLCT is characterized by the presence of irregular anastomosing tubules lined by cuboidal or columnar cells [28]. Tumours with this morphology account for 18% of SLCT [31] and they are significantly more likely to be endocrinologically active [32]. SLCT tumors with a retiform pattern pose difficult diagnostic problems, with the majority being misinterpreted as serous papillary cystadenocarcinoma and endodermal sinus tumor. Central pathology review is mandatory to ensure accuracy of diagnosis [33].

SLCT is linked to DICER1 loss of function mutations, whether somatic or germline, in over 90% of cases. The DICER1 gene is responsible for the regulation of gene expression through the production of mature microRNA (miRNA). When functional, DICER has been demonstrated to play a role in ovarian fertility in murine models. It is expressed by granulosa cells and when reduced is associated with a reduced ovulation rate, infertility and loss of ovarian function [34]. Germline DICER1 mutation is associated with a high-risk syndrome for multiple tumour types including pleuropulmonary blastoma (PPPB), cystic nephroma, childhood embryonal rhabdomyosarcoma, Wilms tumour, nodular thyroid hyperplasia, thyroid carcinoma and SLCT [34]. In addition to multiple tumours, DICER1 mutations are associated with renal and ureteral abnormalities in 6–18% of carriers [28].

Somatic mutation of DICER1 have been identified in 63% of SLCT [8]. When both germline and somatic mutations were assessed then 69% of patients were found to have a germline mutation with or without a somatic abnormality and an additional 29% were found to have a somatic only mutations [12]. The rate of tumour DICER1 mutation was found to be similar in both intermediately differentiated and poorly differentiated tumors, however, well differentiated were far less likely to be found with this mutation.

Q. Discuss Prognosis for Sertoli Leydig Cell

Up to 97% of SLCT tumours present as stage 1 disease with the majority (60–85%) being stage 1A at diagnosis [28]. Overall outcome in SLCT is strongly correlated with stage at diagnosis, histological grade and the presence of heterologous elements or retiform pattern. Advanced stage, capsule rupture, heterologous elements and retiform pattern are poor prognostic indicators and should be considered as high-risk markers of disease [8]. Surgery is the mainstay of treatment; however radical surgery is not always required. SLCT are often diagnosed in young women with disease confined to the ovary, in view of this a fertility sparing surgery ought to be considered. The type of surgery, whether radical or fertility sparing does not influence the recurrence free or overall survival of women with stage 1A disease with recurrence of 8% vs 3% in radical surgery and fertility sparing surgery respectively [27]. At staging surgery, even if fertility sparing, lymph node assessment is not advocated due to the rarity of lymph node involvement [8]. SLCT may be associated with a germline DICER1 mutation, therefore it is important to be aware of the risk of ureteral abnormalities in these patients. For surgeons performing staging operations with any retroperitoneal procedures, specific focus ought to be maintained to minimize the risk of ureteral damage. Pre-operative ultrasound of the renal tract may aid in planning surgery and avoiding complications [28]. Surgery is an important tool in recurrence and should be performed for locally confined recurrent disease [8].

In stage one disease the overall survival is extremely good at 92%, however, this does considerably drop if more advanced disease is present. Five-year overall survival for stage II to IV is only 67% [32]. Tumour recurrence has been identified in 16–35% of all SLCT [12]; with recurrence rates of 74–100% of those diagnosed with greater than stage 1 disease. The overall risk of recurrence in stage 1A SLCT is low at 7%, compared with 30–60% risk of recurrence in stage 1C disease demonstrating the significance of ovarian capsule status in SLCT [27]. Recurrence is more frequently associated with higher grade tumours and those identified with heterologous elements and retiform pattern [8, 27, 32]. Of those who recurred between 50–79% died of disease progression [27, 31].

Presence of germline DICER1 mutation is associated with better recurrence free survival and overall survival. Somatic DICER1 mutation did not impact survival. Patients with a germline DICER1 mutation are however at an increased risk of metachronous tumours in the contralateral ovary. These metachronous tumours behave differently to recurrence tumors with a more favorable prognosis. Patients with an identified germline mutation should have careful scrutiny of any subsequent disease to identify whether this

is metachronous or recurrence. These metachronous tumors can occur decades after primary diagnosis therefore long term follow up in germline DICER1 mutation carriers is appropriate [31]. Due to the high-risk syndrome associated with DICER1 germline mutations, consideration of germline mutation screening and further genetic counselling should be considered for any patient diagnosed with an SLCT tumour and other high-risk factors (e.g. previous thyroid nodules).

Q. What Is the Recommended Adjuvant Treatment?

Due to the rarity of the disease there is no established clinical evidence about the true benefits of adjuvant chemotherapy in SLCT. As the SLCT can behave aggressively adjuvant chemotherapy may be recommended in high risk histological variants of SLCT. The most common regime used is Bleomycin, Etoposide and Cisplatin (BEP) or a combination of carboplatin and paclitaxel due to the similar level of efficacy [8, 32]. The benefit of adjuvant chemotherapy in primary disease has not been conclusively demonstrated but there is evidence of the utility of adjuvant chemotherapy in recurrent disease [8]. Currently chemotherapy is recommended for patients with stage 1C or above disease, and those with high risk factors (poor differentiation, heterologous elements and retiform pattern [27, 28]. The need for chemotherapy in stage 1A tumours with intermediately differentiated morphology without heterologous elements or retiform pattern remains unclear. Data currently available does not show any obvious benefit in this circumstance [28]. Adjuvant therapeutic planning may be complicated in women with DICER1 who develop subsequent tumours after initial diagnosis. As metachronous tumours behave in a less aggressive fashion than recurrence, careful assessment of tumour type will be needed in disease management. Metachronous disease may be more sensitive to first line chemotherapy than recurrent disease, therefore accurately making the distinction is of the utmost importance [31].

Key Points

1. Stromal cell tumours of the ovary are not common and need expert histological assessment for accurate diagnosis.
2. Juvenile and adult granulosa cell tumour have distinct clinical outcomes and it is imperative to distinguish them histologically. FOXL2 mutations are common in adult GCT which are distinctly absent in juvenile GCT
3. Adjuvant chemotherapy is being recommended for all stage of granuolsa cell tumour which are greater than stage 1A.
4. Hormonal treatment with aromatase inhibitors, GnRH therapy and SERMs is being increasingly used in recurrent cancer to slow progression rate and enhance operability.
5. Late recurrences are not uncommon with GCT and Inhibin B and AMH levels are regularly assessed to exclude recurrence
6. Sertoli Leydig cell tumour maybe estrogen or androgen producing and may therefore present with estrogen related symptoms or with androgenization/virilizing symptoms
7. Surgery remains the mainstay of treatment and adjuvant chemotherapy maybe recommended for histologically aggressive variants or higher stage disease.
8. Germline DICER1 mutations are common in SLCT and these carry a better prognosis.

References

1. Maoz A, Matsuo K, Ciccone MA, Matsuzaki S, Klar M, Roman LD, et al. Molecular pathways and targeted therapies for malignant ovarian germ cell tumors and sex cord-stromal tumors: a contemporary review. Cancers (Basel). 2020;12(6):1398.
2. Canario R, Lima JP, Migali C, Tunariu N, George A, Kaye SB, et al. 877PD-clinical outcomes of recurrent ovarian granulosa cell tumours treated with letrozole: a 10-year retrospective case-series of the Royal Marsden Hospital. Ann Oncol. 2014;25(4):iv305.
3. Korach J, Perri T, Beiner M, Davidzon T, Fridman E, Ben-Baruch G. Promising effect of aromatase inhibitors on recurrent granulosa cell tumors. Int J Gynecol Cancer. 2009;19(5):830–3.
4. Li J, Chu R, Chen Z, Meng J, Yao S, Song K, Kong B. Progress in the management of ovarian granulosa

cell tumor: a review. Acta Obstet Gynecol Scand. 2021;100(10):1771–8.
5. Dridi M, Chraiet N, Batti R, Ayadi M, Mokrani A, Meddeb K, Yahiaoui Y, Raies H, Mezlini A. Granulosa cell tumor of the ovary: a retrospective study of 31 cases and a review of the literature. Int J Surg Oncol. 2018;2018:4547892.
6. El Helali A, Kwok GST, Tse KY. Adjuvant and post-surgical treatment in non-epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2022;78:74–85.
7. Alhilli MM, Long HJ, Podratz KC, Bakkum-Gamez JN. Aromatase inhibitors in the treatment of recurrent ovarian granulosa cell tumors: brief report and review of the literature. J Obstet Gynaecol Res. 2012;38(1):340–4.
8. Akman L, Ertas IE, Gokcu M, Terek MC, Sanci M, Sanli UA, Zekioglu O, Ozsaran AA. Ovarian sertoli-leydig cell tumors: a multicenter long-term clinicopathological analysis of 27 patients. J Cancer Res Ther. 2016;12(1):290–4.
9. Aust S, Eberst L, Tredan O, Rousset-Jablonski C, Treilleux I, Méeus P, et al. Detailed overview on rare malignant ovarian tumors. Bull Cancer. 2020;107(3):385–90.
10. Jamieson S, Fuller PJ. Molecular pathogenesis of granulosa cell tumors of the ovary. Endocr Rev. 2012;33(1):109–44.
11. Ndhlovu E, Liu L, Dai J, Dong X, Zhang W, Chen B. Retrospective analysis of clinicopathological characteristics of 19 ovarian juvenile granulosa cell tumor cases. J Obstet Gynaecol Res. 2021;47(7):2492–9.
12. Schultz KAP, Harris AK, Finch M, Dehner LP, Brown JB, Gershenson DM, et al. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol. 2017;147(3):521–7.
13. Wu H, Pangas SA, Eldin KW, Patel KR, Hicks J, Dietrich JE, Venkatramani R. Juvenile granulosa cell tumor of the ovary: a clinicopathologic study. J Pediatr Adolesc Gynecol. 2017;30(1):138–43.
14. Hansen R, Lewis A, Sullivan C, Hirsig L. Juvenile granulosa cell tumor diagnosed in 6-month-old infant with precocious puberty. Radiol Case Rep. 2021;16(9):2609–13.
15. Meisel JL, Hyman DM, Jotwani A, Zhou Q, Abu-Rustum NR, Iasonos A, Pike MC, Aghajanian C. The role of systemic chemotherapy in the management of granulosa cell tumors. Gynecol Oncol. 2015;136(3):505–11.
16. Inada Y, Nakai G, Yamamoto K, Yamada T, Hirose Y, Terai Y, Ohmichi M, Narumi Y. Rapidly growing juvenile granulosa cell tumor of the ovary arising in adult: a case report and review of the literature. J Ovarian Res. 2018;11(1):100.
17. Yang A, Curtin J, Muggia F. Ovarian adult-type granulosa cell tumor: focusing on endocrine-based therapies. Int J Endo Oncologia. 2018;5(2) https://doi.org/10.2217/ije-2017-0021.
18. van Meurs HS, van Lonkhuijzen LR, Limpens J, van der Velden J, Buist MR. Hormone therapy in ovarian granulosa cell tumors: a systematic review. Gynecol Oncol. 2014;134(1):196–205.
19. Banerjee SN, Tang M, O'Connell RL, Sjoquist K, Clamp AR, Millan D, et al. PARAGON Investigators. A phase 2 study of anastrozole in patients with oestrogen receptor and/progesterone receptor positive recurrent/metastatic granulosa cell tumours/sex-cord stromal tumours of the ovary: the PARAGON/ANZGOG 0903 trial. Gynecol Oncol. 2021;163(1):72–8.
20. Färkkilä A, Koskela S, Bryk S, Alfthan H, Bützow R, Leminen A, et al. The clinical utility of serum anti-Müllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors--A comparative study with inhibin B. Int J Cancer. 2015;137(7):1661–71.
21. Fotopoulou C, Savvatis K, Braicu EI, Brink-Spalink V, Darb-Esfahani S, Lichtenegger W, Sehouli J. Adult granulosa cell tumors of the ovary: tumor dissemination pattern at primary and recurrent situation, surgical outcome. Gynecol Oncol. 2010;119(2):285–90.
22. Bennetsen AKK, Baandrup L, Aalborg GL, Kjaer SK. Non-epithelial ovarian cancer in Denmark - incidence and survival over nearly 40 years. Gynecol Oncol. 2020;157(3):693–9.
23. Zhao D, Zhang Y, Ou Z, Zhang R, Zheng S, Li B. Characteristics and treatment results of recurrence in adult-type granulosa cell tumor of ovary. J Ovarian Res. 2020;13(1):19. https://doi.org/10.1186/s13048-020-00619-6.
24. Nasioudis D, Ko EM, Haggerty AF, Giuntoli RL 2nd, Burger RA, Morgan MA, Latif NA. Role of adjuvant chemotherapy in the management of stage IC ovarian granulosa cell tumors. Gynecol Oncol Rep. 2019;28:145–8.
25. Mangili G, Sigismondi C, Maoz A, Matsuo K, Ciccone MA, Matsuzaki S, et al. Molecular pathways and targeted therapies for malignant ovarian germ cell tumors and sex cord-stromal tumors: a contemporary review. Cancers (Basel). 2020;12(6):1398.
26. Frigerio L, Candiani M, Savarese A, Giorda G, Lauria R, Tamberi S, Greggi S. Recurrent granulosa cell tumors (GCTs) of the ovary: a MITO-9 retrospective study. Gynecol Oncol. 2013;130(1):38–42.
27. Gouy S, Arfi A, Maulard A, Pautier P, Bentivegna E, Leary A, Chargari C, Genestie C, Morice P. Results from a monocentric long-term analysis of 23 patients with ovarian Sertoli-Leydig cell tumors. Oncologist. 2019;24(5):702–9.
28. Durmuş Y, Kılıç Ç, Çakır C, Yüksel D, Boran N, Karalök A, Boyraz G, Turan AT. Sertoli-Leydig cell tumor of the ovary: analysis of a single institution database and review of the literature. J Obstet Gynaecol Res. 2019;45(7):1311–8.
29. van Meurs HS, van der Velden J, Buist MR, van Driel WJ, Kenter GG, van Lonkhuijzen LR. Evaluation of response to hormone therapy in patients with measurable adult granulosa cell tumors of the ovary. Acta Obstet Gynecol Scand. 2015;94(11):1269–75.

30. Schwartz M, Huang GS. Retreatment with aromatase inhibitor therapy in the management of granulosa cell tumor. Gynecol Oncol Rep. 2015;15:20–1.
31. Schultz KAP, Harris AK, Finch M, Dehner LP, Brown JB, Gershenson DM, Young RH, Field A, Yu W, Turner J, Cost NG, Schneider DT, Stewart DR, Frazier AL, Messinger Y, Hill DA. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol. 2017;147(3):521–7.
32. Wang G, Zhang R, Li C, Chen A. Characteristics and outcomes analysis of ovarian Sertoli-Leydig cell tumors (SLCTs): analysis of 15 patients. J Ovarian Res. 2021;14(1):150.
33. Kawatra V, Mandal S, Khurana N, Aggarwal SK. Retiform pattern of Sertoli-Leydig cell tumor of the ovary in a 4-year-old girl. J Obstet Gynaecol Res. 2009;35(1):176–9.
34. Conlon N, Schultheis AM, Piscuoglio S, Silva A, Guerra E, Tornos C, Reuter VE, Soslow RA, Young RH, Oliva E, Weigelt B. A survey of DICER1 hotspot mutations in ovarian and testicular sex cord-stromal tumors. Mod Pathol. 2015;28(12):1603–12.

10 Borderline Ovarian Tumours: Early and Advance Stage: Serous, Mucinous, Micro Invasive Cancer, Invasive Implants

Kavita Singh and Bindiya Gupta

Introduction

Borderline ovarian tumours (BOT) or atypical proliferative tumor are neoplasms of epithelial origin characterized by increased cellular proliferation, mild nuclear atypia without destructive stromal invasion. These account for 10–15% of all epithelial tumours. Based on the epithelial cell type, BOT are classified into six types: serous (50%), mucinous (45%), and less common subtypes including endometrioid, clear cell, seromucinous, and borderline Brenner tumor. Bilateral tumors represent about 30%, and about 70% are confined to one or both ovaries (stage I) at the time of diagnosis [1]. Mucinous borderline tumors are further divided into two subtypes: the intestinal type (85–90%) and the endocervical type (10–15%). The intestinal type ae good prognostic tumors seen in older age, are usually unilateral large multilocular cysts, and are associated with pseudomyxoma peritonei. The endocervical type are more aggressive, occurs in younger women, may be bilateral (20–30%), present as unilocular cystic tumor, and are associated with a poorer prognosis as they present in advanced stage, and are associated with implants or lymph node metastasis [2]. Mucinous BOT can be primary or metastatic, usually from GI tract. Primary mBOT may be associated with other ovarian neoplasms like brenner tumor, mucinous cystadenofibroma, teratoma ort endometriosis.

Histological criteria for the diagnosis include nuclear atypia, stratification of the epithelium, formation of microscopic papillary projections and the absence of stromal invasion.

K. Singh (✉)
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_10

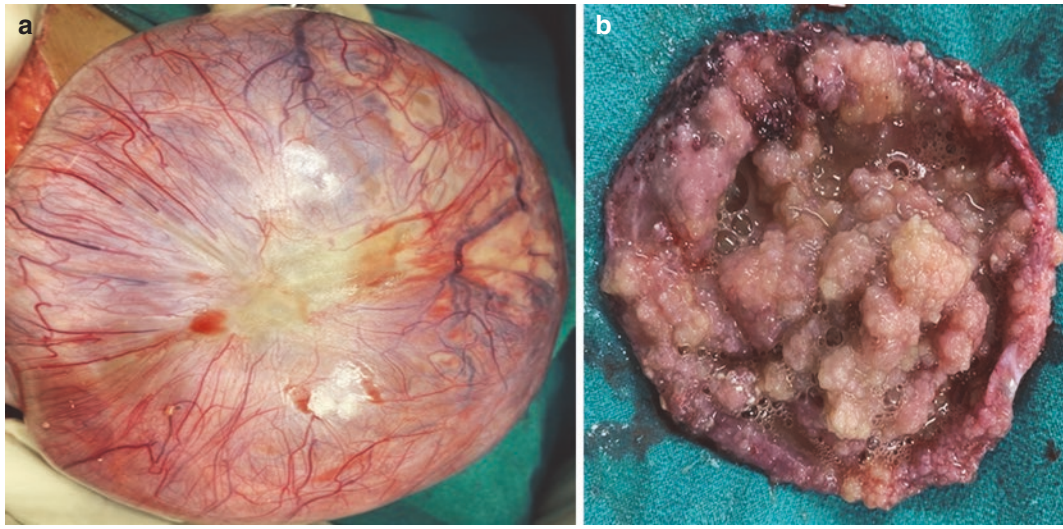


Fig. 10.1 (**a**) Intraoperative image showing a large cystic mass with intact capsule, no surface excrescences. (**b**) Cut section showing multiple papillary projections in the inner surface of ovary

In this chapter we shall discuss some case presentations of borderline ovarian cancer (Fig. 10.1).

Case 1: Serous Borderline Ovarian Tumour

Age, Parity, PS	24 years, Nulliparous, Undergoing tt. for primary infertility, PS = 0
Presenting complaints	26 weeks size cystic mass arising from left adnexa
Co morbidities	Nil
Transvaginal sonography	Ultrasound: Bilateral complex ovarian masses; left side 10 × 8 cm; right side 6 × 8 cm
Other investigations	CE MRI: 12X10X11 cm cystic mass left ovary with papillary projections +, mild free fluid, omental thickening +, no RP nodes Tumour markers: CA125: 59 U/ml, CEA: 1.6 ng/ml, AFP: 1.8 ng/ml, LDH: 187 U/L BHCG: 2 mIU/ml
Surgery	Counselled for fertility preserving surgery Staging laparotomy – peritoneal cytology + left salpingo oophorectomy + infracolic omentectomy + peritoneal biopsies
Histology	Frozen section: s/o borderline tumor Serous borderline ovarian tumor, stage 1A

Q. Diagnostic Indicators for BOT on Clinical Presentation and Imaging

Borderline ovarian tumors are slow growing and seen in a relatively younger population compared to high grade tumours; 50% occur in women less than 40 years of age. They can be asymptomatic with an incidental diagnosis of an ovarian mass on imaging, or may be associated with symptoms of pelvic pain, dyspareunia, abdominal lump and have an association with infertility.

On ultrasound presence of a bilateral complex ovarian mass with presence of profuse papillary projections may indicate borderline tumor. One of the preoperative diagnostic models given by the International Ovarian Tumor Analysis group (IOTA) is the ADNEX model which not only estimates the risk of malignancy but classifies the tumors as borderline, invasive, according to stage or secondary tumours [3].

Serum CA 125 is rather non-specific. Kolwijck et al. reported that serum CA 125 levels were more often noted in patients with the serous type (67%) than the mucinous type (39%) and in patients with advanced-stage disease (83%) more frequently than in stage I disease (47%) [4] (Fig. 10.2).

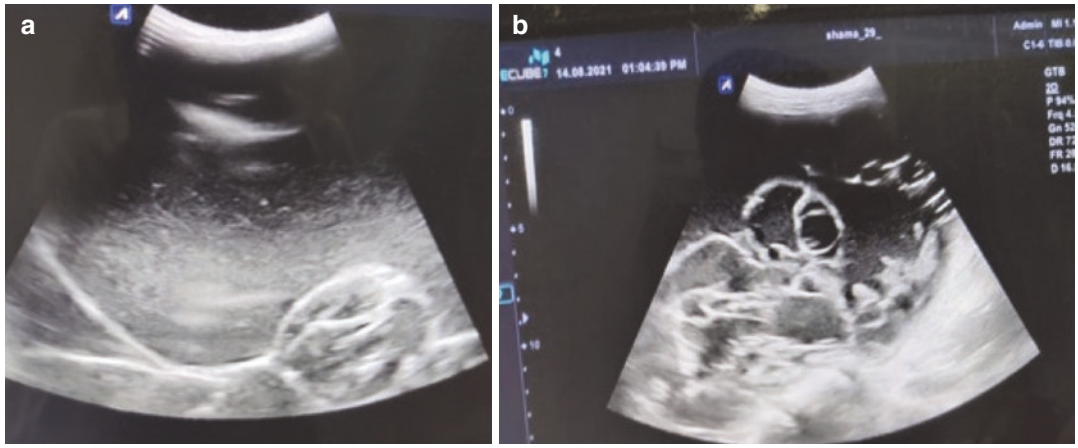


Fig. 10.2 (**a**) Large ovarian cyst, fluid containing low level internal echoes. (**b**) Multiple septations, no increased colour flow, no solid areas

What is the Procedure of Surgical Staging for Borderline Ovarian Tumours

Management of BOT depends on age, type of BOT, stage and desire for fertility preservation. Surgical staging of BOT is similar to that of invasive ovarian cancer. After a midline laparotomy, the peritoneal/ascitic fluid washings are collected followed by the assessment of tumor burden. The aim of surgery is to obtain maximal cyto reduction (R0 resection). Various procedures to attain the surgical goal include hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies and excision of all suspicious lesions and visible disease. Lymphadenectomy is the most controversial issue of the surgery and according to the current consensus routine lymphadenectomy is not necessary in early stage. However, removal of bulky nodes is recommended.

Role of minimally invasive surgery (laparoscopic or robotic) is not clearly established. Factors to be considered in the selection of MIS include size of the ovarian mass(es), extent of tumour metastasis, number and type or previous operations and body habitus. Tumor rupture and contamination of peritoneal cavity must be avoided (Fig. 10.3).

This patient was a nulliparous lady aspiring for fertility conservation. Hence a staging laparotomy with unilateral salpingo oophorectomy was done after counselling.

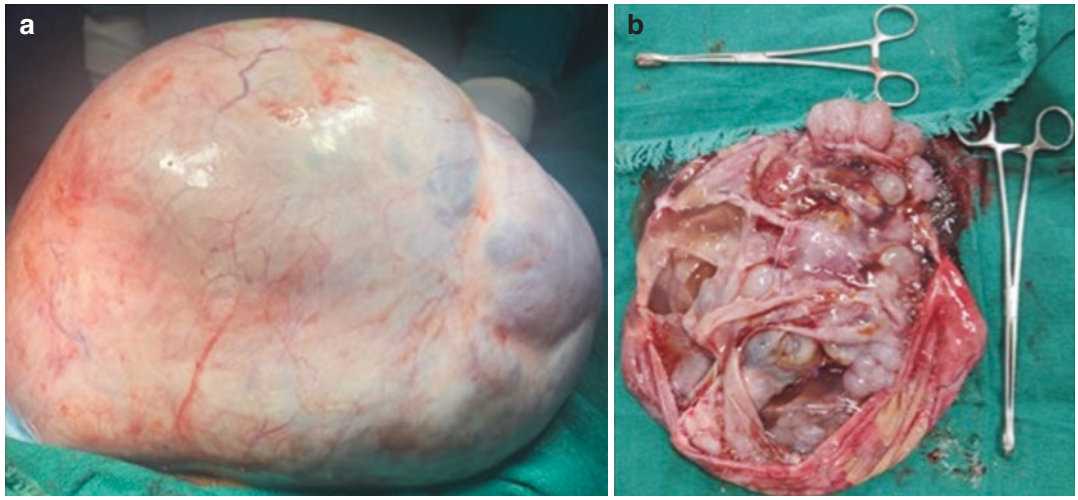


Fig. 10.3 (**a**) Large ovarian mass, intact capsule, no surface excrescences. (**b**) Cut section shows multiloculated mass containing mucin

Q. Role of Frozen Section in Surgery for Borderline Ovarian Masses

The role of intraoperative frozen section in BOT is limited. Frozen section is not advisable as it can only accurately predict in 65% of cases, in 20% it can be upstaged to invasive cancer while in 25% it can even turn out to be benign [5].

Hence any decision based on frozen section may lead to under treatment or overtreatment in the young women. Thus a two staged surgical approach is preferable and decision should only be made after the final histology on central pathology review. A central pathology review is crucial as in 10% cases the diagnosis of borderline may be revised and this has a strong impact in management.

Q. Approach for Fertility Preservation in Bilateral Tumours

Upto 30% of serous BOT are bilateral, hence in this situation it is acceptable that oophorectomy is performed for the larger tumor, while a cystectomy can be done where the tumor is smaller is size. In addition, some authors adopt a more conservative approach and perform bilateral cystectomy in bilateral sBOT for patients who want to preserve childbearing capacity, because no significant difference is seen in recurrence rate compared to USO with contralateral cystectomy. During cystectomy, tumor rupture/ spill is avoided. In both the situations, thorough counselling is required and the patient needs to be explained that recurrence after oophorectomy is around 5% while after cystectomy is 30–40% [6]. However, majority of the recurrences are borderline which can be salvaged surgically.

Q. Role of Surgical Restaging in Patients Who Are Incompletely Staged

The role of surgical restaging is controversial as it has more prognostic value rather than a therapeutic value or improved survival. 15% of patients are only upstaged following a repeat surgery [7]. The patient needs to be counselled and should be made to understand the prognosis and risk of recurrence. In both the situations the patient will be put on surveillance and majority of recurrences are usually borderline.

Minimally invasive approach can be considered while taking the decision for restaging.

Q. Invasive and Non Invasive Implants: How to Diagnose and Their Management

Implants are seen on the peritoneal surface and appear as epithelial cell implants or desmoplastic implants. Implants with invasion of underlying tissue or omental fat were classified invasive implants in the previous WHO classification, however BOT with invasive implants have been redesignated as low grade serous carcinoma (LGSOC) [8].

Patients with peritoneal implants, those with invasive implants appear to have a higher relapse rate (> 50%) and worse prognosis than those with non-invasive implants (20–50%) [9]. In a meta analysis of 4129 patients, Seidman et al. reported an overall survival of 95–100% with non invasive implants and 66% with invasive peritoneal disease (LGSC).

Q. Management of Recurrence

In recurrent tumours the factors that need to be considered for secondary cytoreduction include age, comorbidities and tumour distribution. In cases where surgical cytoreduction is feasible it should be the first line of treatment and aim should be to achieve R0 resection.

However, if the distribution of disease is very extensive or not feasible due to co morbidities, fine-needle aspiration/core biopsy is necessary for an accurate histologic diagnosis. If it is reported as low grade serous or high-grade serous carcinoma, then chemotherapy should be considered.

Q. Discuss Role of Adjuvant Chemotherapy in Borderline Tumours

Borderline tumours have a low proliferation rate and studies fail to show any survival benefit with post operative chemotherapy or hormone therapy in cases with invasive or non invasive implants [10]. Although >90% of serous BOT have estrogen receptors, role of post op tamoxifen or letrozole has not been established.

Q. Follow Up and Prognosis of Serous BOT. Role of Completion Surgery Once Family is Complete

The prognostic factors are FIGO stage, presence of invasive implants, micropapillary pattern, microinvasion, incomplete surgical staging, residual disease, high preoperative CA125 levels [11]. The 5-year survival rate for stage I BOTs is approximately 95% to 97%, and even patients presenting with stage II to III BOTs have 5-year survival rates of 65% to 87% [12].

Majority of recurrences occur in the first 2 years around 10–15%. The follow up visits are every 3–4 months in first 2 years and six monthly next 3 years. For patients who undergo fertility-sparing surgery, particularly those with stage I serous borderline tumours, the major concern is for the residual ovary. If such patients develop a ‘recurrence’, it is almost always an actual separate primary borderline tumour in the residual ovary. Upto 4–7% of women with SBT develop subsequent carcinoma, usually low grade but rarely high grade. The risk factors include micropapillary subtype, advanced stage, bilaterality, ovarian surface involvement and residual disease after surgery.

Surveillance includes detailed history and physical examination at each visit, sonography if fertility-sparing surgery was performed and serum tumour markers CA 125 and/or CEA for mucinous histology. Tumor markers are more relevant if they were initially elevated. In case the patient develops a significant elevation of a tumour marker, or has suspicious physical findings ultrasound/CECT is suggested.

Completion surgery is not recommended after completion of family as recurrences are usually borderline and patient can be kept on close follow up.

In this case the patient is on follow up and has been sent to a fertility specialist. Re valuation of ovarian reserve (AMH levels) will be done at 6 months and accordingly a decision will be made for natural/ assisted conception. Spontaneous pregnancy rates are around 30–80%.

Case 2: Mucinous Borderline Ovarian Tumours

Age, Parity, PS	69 years P1 + 0 PS = 2. BMI 23
Presenting complaints	Clinical presentation: Abdominal mass
Co morbidities	Non Hodgkin's lymphoma in remission, chronic kidney disease on mycophenolate mofetil (MMF), moderate COPD, arthritis, gout
Transvaginal sonography	**Ultrasound:** Bilateral complex ovarian masses; left side 15 × 19 cm; right side 6 × 8 cm
Other investigations	**Tumour markers:** CA125: 55 KU/L, CA19-9: 92 KU/L, CEA: 3 μg/L CECT abdomen + pelvis:
Surgery	Staging laparotomy: Peritoneal cytology + bilateral Salpingo oophorectomy + hysterectomy + infracolic omentectomy
Histology	Left ovary: Borderline mucinous ovarian tumor, right ovary fibroma Cytology and omental biopsy negative CK7+ve, focal CK20 and CDX2 FIGO stage Ia
Further management	Patient initiated follow up. No further GI investigation required as metastatic mucinous borderline tumor ruled out on histology and IHC

Table 10.1 Difference between serous and mucinous borderline tumours

Features	Mucinous BOT	Serous BOT
Incidence	35–45% (>1/3rd of all BOT)	50% (2/3rd of all BOT)
Implants	Less common usually non invasive Presence of implants may indicate metastatic disease	33% (invasive and non invasive) Invasive implants are re-categorised as low grade serous cancers
Recurrence rate and type of recurrence	3.6%, more often invasive recurrence	18.3–19.9%, generally non invasive except in micro papillary pattern
Bilateral	7%	33%
Mutations	KRAS mutations (92%- 60%) of MBT	KRAS and BRAF mutations are each present in about 30% of SBT
Origin of tumours	Can be primary or metastatic from GI	Usually primary ovarian
Stage	Usually present in early stage; advanced stage at presentation is uncommon	Can present in both early and advanced stage

Q. What is the Difference Between Serous and Mucinous BOT

The difference between serous and mucinous borderline tumours is shown in Table 10.1.

Q. What Are the Diagnostic Indicators i.e. Clinical Presentation, Imaging and Tumor Marker Evaluation for Mucinous Borderline Ovarian Tumors?

These are slow growing tumours seen in a relatively younger population compared to high grade tumours; 50% are seen in women less than 40 years of age. Clinical presentation is similar to serous BOT, except that masses are larger in size. Other symptoms of presentation are pelvic pain, dyspareunia and abdominal lump.

On ultrasound borderline tumours may appear as multi-loculated cysts to complex ovarian mass. CT scan or MRI is usually done in all cases following detection of an ovarian mass with suspicious features. Cross sectional imaging helps in assessment of ovarian mass and exclusion of metastatic disease and retroperitoneal nodal enlargements.

Besides germ cell tumor markers, CA125, CEA and CA19-9 should be done in all cases.

Borderline mucinous tumour after bilateral salpingo-oophorectomy recurrence rates are very low.

Hysterectomy was declined by the patient as she wanted only minimal surgery because of her medical comorbidities.

Q. Compared to Serous BOT What Is the Difference in Surgical Staging?

Compared to serous BOT's mucinous BOT are less frequently seen in advanced stages (24.1% versus 3.8%) [13]. All attempts should be made towards complete cytoreduction and to remove all visible disease to improve prognosis. In contrast to invasive disease, peritoneal implants are small, hence obviating the need for complex surgical resections or bowel resections. In young women with peritoneal implants, a normal contralateral ovary may be preserved.

Appendicectomy should be performed only when the appendix is grossly abnormal.

Case 3: Serous Borderline Tumor with Microinvasion

Age, Parity, PS	32 years, P1 + 0, keen on conception, PS = 0
Presenting complaints	**Symptoms:** Abdominal pain, distension, urinary frequency **Examination:** Abdominal mass 16 weeks' size
Co morbidities	None
Transvaginal sonography	**Ultrasound:** Bilateral complex ovarian masses; left side 10 × 8 cm; right side 6 × 8 cm
Other investigations	**Tumour markers:** CA125: 32 KU/L, CA19-9: 78KU/L, CEA: 5 μg/L, BHCG, AFP negative
Surgery	Laparoscopic bilateral ovarian cystectomy
Histology	Bilateral borderline serous tumours with focal microinvasion in one ovary with surface involvement, FIGO stage 1C2
Further management	Counselled: Completion surgery/ surveillance Keen on surveillance **Follow up (6 months):** MRI: Complex right ovarian cyst 3.2 cm, left side ovarian endometrioma Patient declined any further completion surgery as she was keen for future conception

Q. What Is the Significance of Microinvasion and Micro Papillary Pattern?

Microinvasion in BOT is a histological feature characterized by the presence of small groups of cells or single cells invading the stroma up to 5 mm of greatest linear measurement in any single focus of the ovarian tumor. In a large series of 209 patients with BOT (group 1: 28 with microinvasion and group 2; 181 without microinvasion); relapses occurred in 21.4% of the cases in group 1 and in 12.7% of the cases in group 2 (p = 0.21). Progression-free survival was significantly longer in BOTs compared to microinvasive BOTs (P = 0.041), but overall survival did not differ [14]. Borderline tumour may progress to invasive cancer in 3.7% irrespective of presence of intraepithelial carcinoma and microinvasion [15]. The presence of microinvasion has no prognostic significance and does not require any adjuvant treatment.

Serous borderline ovarian tumors with micropapillary patterns (complex nonhierarchical micropapillae and only mild nuclear atypia with marked epithelial cell proliferation) are more commonly associated with advanced stage, surface ovarian involvement, bilateral ovarian involvement, invasive implants and invasive recurrence than the typical sBOTs [16]. Hence a closer surveillance is warranted and in women with completed families as radical surgical approach should be considered.

Key Points

1. Most common are the serous BOT followed by mucinous subtype. The latter is further classified into the intestinal type (85–90%) and the endocervical type (10–15%).
2. Mucinous BOT can be primary or metastatic, usually from GI tract. Hence metastatic work up should be done in all cases of mucinous BOT
3. Surgery is the mainstay of treatment and complete cytoreduction should be achieved. Fertility preserving surgery can be done in women desirous of further conception.
4. Recurrences are higher with cystectomy compared to salpingo oophorectomy

5. Microinvasive variant and micropapillary pattern increase the chance of recurrence but has no prognostic significance and does not require any adjuvant treatment.

References

1. Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Version 2. Virchows Arch. 2017;470(2):125–42.
2. Lalwani N, Shanbhogue AK, Vikram R, Nagar A, Jagirdar J, Prasad SR. Current update on borderline ovarian neoplasms. AJR Am J Roentgenol. 2010;194(2):330–6.
3. Van Calster B, Van Hoorde K, Valentin L, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ. 2014;349:g5920.
4. Kolwijck E, Thomas CMG, Bulten J, et al. Preoperative CA125 levels in 123 patients with borderline ovarian tumours. Int J Gynecol Can. 2009;19(8):1335–8.
5. Ratnavelu ND, Brown AP, Mallett S, Scholten RJ, Patel A, Founta C, Galaal K, Cross P, Naik R. Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses. Cochrane Database Syst Rev. 2016;3(3):CD010360.
6. du Bois A, Ewald-Riegler N, du Bois O, Harter P. Borderline tumours of the ovary: a systematic review. Geburtshilfe Frauenheilkd. 2009;69:807–33.
7. Zapardiel I, Rosenberg P, Peiretti M, et al. The role of restaging borderline ovarian tumours: single institution experience and review of the literature. Gynecol Oncol. 2010;119(2):274–7.
8. WHO Classification of tumours. Female genital tumours. 5th ed. 2020.
9. Gershenson DM. Clinical management potential tumours of low malignancy. Best Pract Res Clin Obstet Gynaecol. 2002;16(4):513–27.
10. Vasconcelos I, Olschewski J, Braicu I, Sehouli J. A meta-analysis on the impact of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors with invasive implants. Oncologist. 2015;20:151–8.
11. Gershenson DM. Management of borderline ovarian tumours. Best Pract Res Clin Obstet Gynaecol. 2017;41:49–59.
12. Tropé C, Davidson B, Paulsen T, Abeler VM, Kaern J. Diagnosis and treatment of borderline ovarian neoplasms "the state of the art". Eur J Gynaecol Oncol. 2009;30(5):471–82.
13. du Bois A, Ewald-Riegler N, de Gregorio N, et al. Borderline tumours of the ovary: a cohort study of the Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. Eur J Cancer. 2013;49(8):1905–14.
14. Ferrero A, Strada I, Di Marcoberardino B, et al. Clinical Significance of Microinvasion in Borderline Ovarian Tumors and Its Impact on Surgical Management. Int J Gynecol Can. 2012;22:1158–62.
15. Vasconcelos I, Darb-Esfahani S, Sehouli J. Serous and mucinous borderline ovarian tumours: differences in clinical presentation, high-risk histopathological features, and lethal recurrence rates. BJOG. 2015;123(4):498–508.
16. Malpica A, Longacre TA. Prognostic indicators in ovarian serous borderline tumours. Pathology. 2018;50(2):205–13.

Part II

Case Based Studies: Cervical Cancer

Early Stage Cervical Cancer

11

Bindiya Gupta and Namita Batra

Introduction

Cervical cancer is the fourth most cancer among women globally and second most common malignancy in women in low-resource countries with incidence of 15.7% per 100.000 females. In 2020, there were estimated 604,000 new cancer cases and 342,000deaths worldwide, with 90% of cases from low and middle income countries [1]. Human papilloma virus is central to the development of this cancer and is detected in more than 95% of cases. Squamous cell carcinoma is the most common histologic type (70%) followed by adenocarcinoma (25%). Although surgery is the standard of care for cervical cancer in early stages, it is important to understand the differences in the extent of surgery especially possibility of more conservative surgery in specific patient groups, preferred surgical approach and lymph node evaluation strategies. The main emphasis is to avoid dual treatment with surgery and radiation which increases the patient morbidity. In this chapter management of early stage cervical cancer cases will be discussed.

B. Gupta (✉)
Department of Obstetrics and Gynecology, UCMS and GTB Hospital, New Delhi, India

N. Batra
Department of Obstetrics and Gynecology, UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_11

Case 1: FIGO Stage IA1

Age, parity, PS	28 years, P1+0, PS-0
Clinical presentation	Intermenstrual bleeding/post coital bleeding x3months Copper coil in situ for the last 9 years, removed 2 months prior to consultation No previous smear test, STI swabs negative for infection Smoker(10/day) Examination: Ectopy present on the posterior lip of cervix
Co morbidities	Nil
Cervical screening	Pap smear: High grade dyskaryosis, HPV+
Transvaginal sonography	Endometrial thickness 16 mm, bilateral polycystic ovaries
Endometrial biopsy	Normal menstrual endometrium
LLETZ	Cone shaped tissues 15X12X11mm depth: CIN3 in all blocks and all margins, HPV associated changes present. No LVSI. CIN3 with crypt involvement. Single superficial focus of invasive squamous cell cancer (1mm × 0.5 mm in depth). Grade could not be assessed (Gx)
Repeat LLETZ	An irregular strip of cervical tissue measuring 25X12mm to a depth of 8 mm: No presence of any residual disease. HPV associated changes, CIN, SMILE, CGIN absent.
Plan	Follow up smear in 6 months and 12 months followed by annual smears for next 9 years

Q. Diagnostic Methods and Their Interpretation for Cervical Cancer

An excisional procedure [Large Loop Excision of Transformation Zone (LLETZ)/conization] is performed in patients with smears showing high grade dyskaryosis/suspicious invasive smears in association with abnormal colposcopic findings to treat CIN and also to exclude invasive carcinoma. In overt/visible growth on cervix, a small loop biopsy or cervical punch biopsy is taken to confirm the diagnosis. Care has to be taken to have sufficient depth of biopsy to assess stromal invasion which is diagnostic of invasive cancer. An adequate biopsy for histologic reporting should be more than 2 mm in maximum dimension, intact and not fragmented and should not have crush artifact. Large sized loops should be avoided if there is presence of obvious growth on cervix as may interfere with interpretation of further MRI findings and result in over staging.

In the excisional specimen the invasive tumor is measured in three dimensions in millimeters; two dimensions to record the horizontal spread and third dimension to assess tumor depth or thickness. FIGO 2018 has revised the staging of early stage cervical cancer where only depth of tumor invasion is taken into consideration to differentiate between IA1 (<3 mm), IA2 (≥3 mm-5 mm) and IB1 (>5 mm) tumors [2]. The depth is measured from the base of the epithelium (surface or glandular crypt) from which the carcinoma arises to the deepest point of tumor stromal invasion.

Besides tumor size; histopathologic type, grade of tumor, presence of lymphovascular space invasion (LVSI) and presence of invasive and preinvasive disease on specimen margin is noted. Three margins are primarily assessed: ectocervical, endocervical and deep lateral/radial resection margins. The distance of the carcinoma to the closest excision margins should be recorded and completeness of excision at all margins should be mentioned by the pathologist. Assessment of LVSI is crucial as it has a prognostic value. Quantification of LVSI is debatable as single focus or unifocal LVSI is of doubtful significance in comparison to extensive LVSI. It is not the actual count of foci of LVSI, but the extensiveness of LVSI across all cervical histopathological sections that predicts lymphatic spread and risk of future recurrence. Completeness of excision of other preinvasive lesions should also be mentioned to reduce future chances of re-occurrence. These include presence of Cervical Intraepithelial Neoplasia (CIN) and its grade (low grade/high grade), presence or absence of crypt involvement by CIN, cervical glandular intraepithelial neoplasia (CGIN), stratified mucin producing intraepithelial lesion (SMILE).

In the above case the depth of invasion was <3 mm, the staging was Ia1 with no LVSI with

preinvasive disease involving the excision margins, thereby warranting repeat excision.

Q. What Are the Histological Dilemmas in Ia1

Histological assessment of specimen may be impaired by features such as fragmentation, crush or diathermy artefact and epithelial loss. In these cases, it may be difficult to assess if the resection margin is involved or not and assessment of LVSI may be difficult. It is usually separately mentioned in pathology reports and re-excision is recommended if the specimen cannot be orientated, is fragmented, or has diathermy artefact that makes margin assessment impossible.

p16 immuno staining may be used as a surrogate marker for high and intermediate risk HPV types, but it does not correlate with grade of disease. Majority of squamous cell cancers exhibit diffuse block positivity of p16, however some adenocarcinomas can be HPV negative. Alternatively, HPV testing can be done to decide if it is HPV associated or non HPV associated cervical cancer.

Q. What Are the Different Histological Types, Grades of Cervical Carcinoma and Their Prognosis

WHO histological classification of tumors of uterine cervix is shown in Table 11.1. Squamous cell carcinoma (SCC) is the predominant histological type accounting for three-fourths of all cervical cancers. Adenocarcinoma and adenosquamous cell carcinoma represent 10–15%, and other or unspecified histology represent the remaining 10–15%.

Squamous cell cancers are graded according to modified version of Broders as - well differentiated (keratinizing), moderately or poorly differentiated. Grading is based on degree of keratinization, cytonuclear atypia and mitotic activity. Occasionally tumors are too small to be graded (Gx) as in the present case. Adenocarcinoma are graded according to FIGO system of endometrial adenocarcinoma. Grading of adenosquamous carcinoma as - well, moderately, poorly differentiated is according to the degree of differentiation of the squamous and glandular components. Histological types and grading does not influence the prognosis for early stage cervical cancers.

Table 11.1 WHO histologic classification of malignant tumors of uterine cervix

Epithelial tumours: Squamous tumours: Keratinizing, non-keratinizing, basaloid, verrucous, warty, papillary, lymphoepithelioma-like, squamotransitional, early invasive (microinvasive) squamous cell carcinoma Glandular: Adenocarcinoma: Mucinous (endocervical, signet ring cell, intestinal, viloglandular), endometrioid, clear cell, serous, mesonephric Adenosquamous Neuroendocrine tumours: carcinoid, atypical carcinoid, small cell cancer, large cell neuroendocrine carcinoma Glassy cell carcinoma variant Adenoid cystic carcinoma Adenoid basal carcinoma Undifferentiated carcinoma
Mesenchymal tumours: Leiomyosarcoma, endometrial stromal sarcoma, undifferentiated endocervical sarcoma, sarcoma botryoides, angiosarcoma, malignant peripheral nerve sheath tumor
Mixed epithelial and mesenchymal tumours: Carcinosarcoma, adenosarcoma, Wilms tumor, adenofibroma
Melanocytic tumours
Miscellaneous: Germ cell type Lymphoid and hematopoietic Secondary tumors

Endocervical carcinomas are classically HPV related in 80% cases while 20% may be non HPV related. A newer classification, International Endocervical Adenocarcinoma Criteria and Classification (IECC) has divided adenocarcinoma into HPV associated and HPV independent [3]. The histological subtypes which are HPV related are *Usual-type, Villoglandular, Mucinous (intestinal, signet ring and not otherwise specified (NOS)) and Invasive stratified mucin-producing carcinoma (iSMILE).* The non HPV associated (*NHPVA) adenocarcinomas include endometrioid, gastric, clear cell and mesonephric* types. Compared to HPV associated tumours, they have higher prevalence of destructive invasion, extrauterine spread, advanced stage at presentation and lower disease free and overall survival rates [4]. Based on pattern of spread and LVSI, a new 3-tier personalized risk stratification system has been proposed to classify HPV associated endocervical adenocarcinoma (Table 11.2) [4–6]. Neuroendocrine tumors are not graded and

Table 11.2 Pattern based risk stratification system of endocervical adenocarcinoma

Type	Type of glands and pattern of invasion	LVSI	Additional criteria	Lymph node metastasis	Chances of recurrence	Proposed management To be investigated
Pattern A (non destructive invasion)	Well-demarcated glands with rounded contours, frequently forming clusters or groups and sometimes showing relatively well preserved lobular architecture. Tumor glands demonstrate a pushing or **expansile pattern of invasion**	Absent	Lack of solid growth (well-moderately differentiated) no single cells or detachment	0%	0%	Lymph node dissection may be avoided May not need adjuvant therapy Usually stage I
Pattern B (early/focally destructive invasion)	**Localized (limited, early) destructive stromal invasion** arising from pattern A glands	LVSI (present/ absent)	Lack of solid growth (well-moderately differentiated)	<5% (only if LVI +)	<5% (only if LVI +)	Limited lymph node dissection/ sentinel node
Pattern C (diffusely destructive invasion)	**Diffuse destructive stromal invasion**, extensive diffuse desmoplastic response Glands show a destructive (or tentacular) pattern with angulated and often incomplete glands open to the stroma	LVSI (present/ absent)	Confluent growth filling 4× field (5 mm): Glands, papillae or mucin lakes Solid, poorly differentiated component (architecturally high grade)	25%	20%	Radical treatment with nodal resection Usually stage 2 or more

by definition are high grade aggressive tumors with poor prognosis.

Q. Management of Stage IA1 Cervical Cancer

Stage IA1 cancers needs an accurate histological assessment and therefore a central pathology review is desirable along with discussion of each case in centralized gynaecological cancer multidisciplinary team meeting (MDT). Factors to be considered while deciding further treatment after an excisional biopsy include fertility status, excision margin status, presence of LVSI and age of the patient [7].

Careful consenting should be undertaken which involves a detailed counselling about the procedure, risks and its outcomes. Explanation about procedure related risks should include hemorrhage, infection, incomplete excision, cervical stenosis, cervical incompetence and impact on future fertility both in conceiving and continuation of pregnancy with increased risk of late miscarriages and preterm labour.

For tumors with negative histological excision margins (ectocervical, endocervical and radial) with absent LVSI, an excisional procedure (conization/LLETZ) can be considered as a definitive treatment. Patient can be followed up with cervical smear at 6 and 12 months followed by annual smears for 9 years.

A re-excision is recommended in case the margin is positive with invasive or preinvasive disease. Close excision margins of cancer (< 3 mm), fragmented specimen and excessive diathermy artefact make margin assessment difficult and hence, further re-excision is advisable. Repeat LLETZ or cold knife conization can be performed; the latter has an advantage of avoiding thermal artifact for assessment of margins, but requires a general anesthetic and may be associated with higher risk of hemorrhage.

In case re-excision with above surgical techniques is not technically feasible, then treatment with either simple extrafascial hysterectomy or simple trachelectomy (supravaginal excision of cervix) may be recommended. MRI assessment for cervical length is desirable before undertaking simple trachelectomy in these cases and is usually preferred in younger women wishing to preserve their fertility. The re-excision should be performed after 4–6 weeks after the initial treatment as the risk of secondary hemorrhage is twofold to threefold higher if treatment is done within 6 weeks of the first procedure.

In stage Ia1 cervical cancers, in absence of LVSI lymph node assessment is not required as metastasis is detected in less than 1% [8]. However, in presence of extensive LVSI, lymph node assessment can be offered and these patients should ideally be considered for sentinel lymph node assessment as it is associated with reduced morbidity. In centers where sentinel biopsy is not available it is reasonable to offer lymphadenectomy [9].

Q. Significance of Excision Margins in IA1 Adenocarcinoma?

Adenocarcinoma of cervix is unifocal in 85% of cases while 15% can be multifocal. Secondly, the disease is within 10 mm of squamo–columnar junction (SCJ) in less than 35 years while in women older than 35 years it can extend to 20 mm or 25 mm above SCJ. Hence, keeping these in consideration, cone specimen for early stage adenocarcinoma should be cylindrical in shape, should include whole transformation zone and deep glands and extend at least 10 mm in premenopausal women desiring fertility and up to 20–25 mm up the endocervical canal in women with completed family. Loop excision is also acceptable, however efforts should be taken to minimize the effect of diathermy, specimen should not be fragmented and an endocervical curettage should be done after specimen removal to prevent missing of skip lesions [9].

In postmenopausal women endocervical evaluation after excision is difficult and there is cervical stenosis, a simple hysterectomy can be offered.

In this patient CIN 3 was present at margins in the first LLETZ specimen, hence a re-excision was planned. Since the patient was young and intended to have future pregnancies, she was counselled regarding the risk of cervical incompetence, premature labour due to repeat excision. Since there was no residual disease on repeat loop, the patient was counselled and has been on follow up as per local protocol with cervical smears at 6 months, 12 months and annually for 9 years.

Case 2: FIGO Stage IA2

Age, parity, PS	46 years, P2+0, PS-1
Presenting complaints	Asymptomatic with regular menstrual cycles, referred to colposcopy clinic with abnormal PAP smear findings Smoker
Co morbidities	None
PAP smear	High grade dyskaryotic smear
Management	LLETZ done under LA
LLETZ histopathology	Gross specimen: Single piece rectangular cone shaped cervical tissue 30 × 16 × 30 mm, moderately differentiated invasive squamous cell cancer, maximum horizontal dimension 24 mm, depth of stromal invasion: 4 mm, focal LVSI. Invasive tumour lies within 0.5 mm of the ectocervical and deep radial margins. CIN 3 in all five blocks and extension to crypts and ectocervical and radial margins. Endocervical margin clear. HPV associated changes present. Stratified mucin producing intraepithelial lesion of cervix (SMILE): Absent, CGIN absent
Post LLETZ examination	P/S: No obvious growth seen on cervix, evidence of recent LLETZ procedure V/E+, P/R: Normal size uterus, mobile, no adnexa palpable, no parametrial involvement, rectal mucosa free

Q. What Investigations Are Needed for Further Management of the Case?

Traditionally, cross sectional imaging was not required for staging in micro-invasive tumors which was based on the depth of invasion and extent of lateral dimension. However, with adoption of revised FIGO 2018 classification horizontal extent of disease has been disregarded and as a result superficial IB1 have now been shifted to stage 1A2. Therefore, MRI should continue to be performed for all stages of cervical cancers which include IA2 and above as in the present case. MRI is beneficial for assessment of metastasis to lymph node, parametrial/local extension, tumour volume, and assessment of residual cervical length where the fertility preserving surgery is being considered. Tumor volume/residual disease measured on MRI helps in determining radicality of excision.

Besides imaging, routine preoperative investigations including a baseline full blood count, kidney function tests, serum albumin and chest X ray should be done in all cases.

Q. What Is the Further Management of IA2?

Management of Stage IA2 cancers are similar for both squamous and adenocarcinomas. It depends on presence of LVSI, margin status and desire for fertility preservation. Lymph node metastasis is around 4.8% (0–9%) [10]. In revised FIGO 2018 staging, superficial larger size cervical cancers have been included whose risk of lymph node metastasis is unclear, we would therefore recommend at least sentinel node assessment for IA2 cervical cancers with presence of LVSI. In centers not practicing sentinel nodes, it would be recommended to perform traditional pelvic lymphadenectomy if there are associated high risk histological factors identified like extensive LVSI.

Histological findings of LLETZ i.e. margin status, presence of LVSI, decides on further treatment options. Other factors which also influence choice of treatment include patient's fertility desires, age, histological subtypes. Depending on LLETZ findings the management can be decided as given below.

1. LLETZ showing completely excised IA2 cancers and pre-invasive disease with no LVSI (negative endo, ecto and radial margins): Patient can be safely recommended annual cytological surveillance for 10 years or simple hysterectomy.
2. LLETZ showing completely excised IA2 cancers and pre-invasive disease involving the margins: Further excision is required and if margins are clear on second LLETZ for pre-invasive and invasive disease, then cytological follow up for 10 years or simple hysterectomy.
3. LLETZ showing incompletely excised IA2 cancers and invasive disease involving the margins: In this case the tumor is at least 1b1 and a radical hysterectomy with pelvic lymphadenectomy is recommended. MRI should be done to assess the exact dimensions of the tumor. Sentinel lymph nodes can also be offered in institutions where it is an established practice.
4. LVSI positive and completely excised IA2 cervical cancer: Sentinel nodes/pelvic lymphadenectomy should be considered.

Present Case

MRI: Cervix normal, no residual tumor, no parametrial involvement, no pelvic and paraaortic nodes (Fig. 11.1). Impression: FIGO stage IA2 Management: In the present case, tumor dimensions was 24 mm wide and 3.5 mm deep with focal LVSI, a radical hysterectomy plus sentinel nodes ± pelvic lymphadenectomy with bilateral salpingectomy and ovarian conservation was recommended. As the horizontal spread of disease was more than 2 cm and did not fulfill criteria for conservative management as per ConCerv and SHAPE trial protocol
Surgery: Radical hysterectomy with ovarian conservation + pelvic lymphadenectomy
Intraoperative: Uterus normal, cervix no visible growth, scar site healthy, bilateral nodes normal. Findings (Fig. 11.2)
Histopathology: No residual disease on cervix, lymph nodes negative
Follow up: No adjuvant treatment required. Follow up as per network guidance

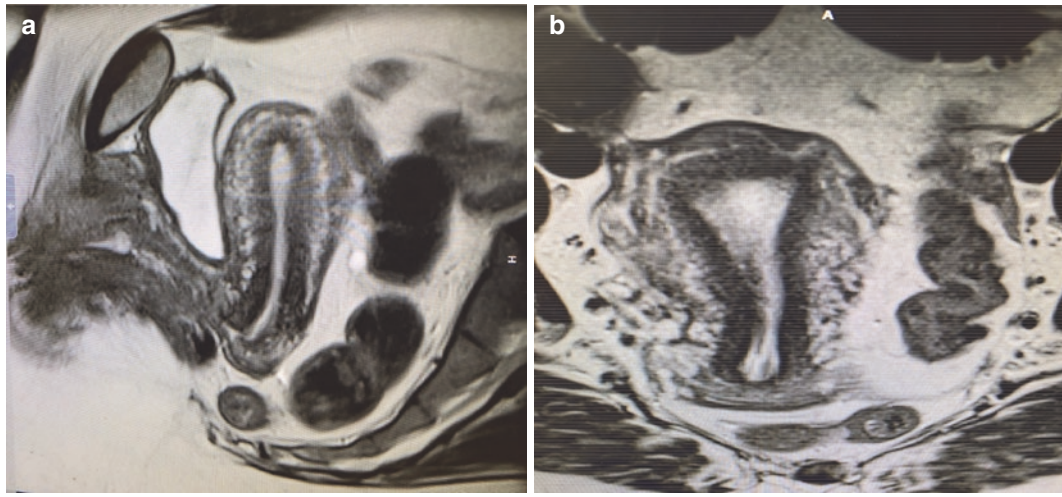


Fig. 11.1 MRI Pelvis: T2 weighted image showing no residual disease and normal parametrium in (**a**) sagittal (**b**) axial sections

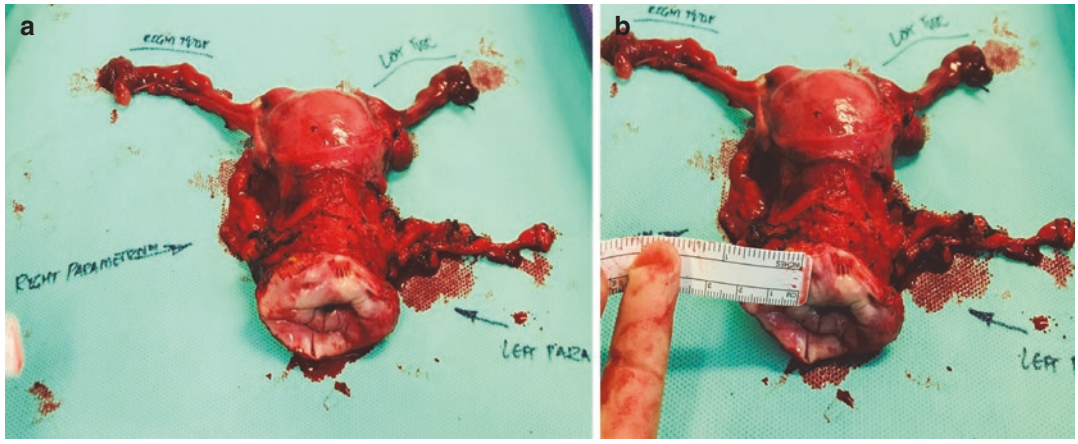


Fig. 11.2 Gross surgical specimen with no visible growth on cervix. 1–2 cm vaginal margins all around the cervix

Q. What Is the Role of Conservative Surgery in Patients with Low-Risk Early-Stage Cervical Cancer?

Early stage cervical cancer (IA2-IB2) has been traditionally been treated with radical hysterectomy. Radical hysterectomy is a more extensive surgery associated with higher intra and post operative complications.

Conservative options like conization, simple hysterectomy or trachelectomy may be considered in selected cases to reduce the morbidity associated with radical hysterectomy while maintaining oncologic safety. Multiple retrospective studies have shown that in early cervical cancer (IA2-IB1) which have favorable pathologic characteristics like tumor size <2cms, no LVSI, depth of invasion <10 mm, squamous cell histology, superficial stromal invasion; the rates of parametrial involvement was low (<1%). The oncologic outcomes were excellent with relapse rate of 0.7% and 0.3% mortality rate. Even with conservative management, patients had undergone sentinel lymph node evaluation or complete pelvic lymphadenectomy [11]. In a systematic review, of 346 patients who underwent conservative surgery the crude recurrence rate was 1.7% and the crude mortality rate was 0.3% [12].

Prospective randomized trial on conservative surgery are summarized in Table 11.3. The results of Concerv trial is showing the feasibility of conservative surgery in selected patients [13]. Additionally, there are two ongoing prospective randomized controlled trials looking at reducing radicality of surgery in early stage histologically low risk cervical cancer, results of which are awaited [14, 15].

Table 11.3 Prospective trials for conservative surgery of cervical cancer

Trial Name	Inclusion criteria	Methods	Results
Conservative surgery of women with low risk early stage cervical cancer (ConCerv) trial (n = 100)	SCC (any grade) or adeno ca (grades 1 or 2) Stage IA2 or IB1; tumor size ≤2 cm; No LVSI, depth of invasion ≤10 mm, negative conisation margins, negative imaging for metastatic disease	**Patients desiring future fertility:** Cervical conization (n = 44) **Patients not desiring future fertility**: Simple hysterectomy (n = 40) Pelvic lymph node dissection with SLN and/or full pelvic lymph node dissection Inadvertent hysterectomy followed by lymph node dissection (n = 16)	Positive lymph nodes were noted in 5%. Residual disease in the post-conization that is, an immediate failure rate of 2.5%. Median follow-up was 36.3 months (range 0.0–68.3). Three patients developed recurrent disease within 2 years of surgery—That is, a cumulative incidence of 3.5% (95% CI 0.9–9.0%) Select patients with early-stage, low-risk cervical carcinoma may be offered conservative surgery
Simple hysterectomy and pelvic node dissection in early-stage low risk cervical cancer (SHAPE) trial	Stage IA2 or IB1; tumor size <2 cm; SCC or adenoCa; stromal invasion <10 mm on LEEP/cone biopsy or < 50% stromal invasion on MRI; all tumor grades and patients with LVSI are eligible	Patients randomized 1:1 **experimental treatment:** Simple hysterectomy (SH) with pelvic lymphadenectomy **Control treatment:** Radical hysterectomy (RH) and pelvic lymphadenectomy SLN mapping optional in both groups	Pelvic recurrence rate for SH was 2.5% versus 2.17% for RH. There were less acute surgery related adverse effects within 4 week of surgery with SH compared to RH (p = 0.4). 3 year extra pelvic recurrence free survival (98.1% versus 99.7%) and overall survival (99.1% versus 99.4%) in SH and RH arms respectively. The rates of adjuvant therapy was similar in two arms (9.2% versus 8.4% in SH and RH arms respectively)
Gynecologic oncology group protocol 278	Stage IA1 (LVSI positive), IA2, or IB1 disease; SCC, adenoca or adenosquamous; Tumor size ≤2 cm Any grade Previous excision procedure with negative margins, depth of invasion < than 10 mm	Patients will be stratified according to their fertility wishes to either cone biopsy and pelvic lymphadenectomy or simple hysterectomy and pelvic lymphadenectomy	Results awaited Outcomes: 1°: Bladder, bowel, and sexual function and to determine the incidence and severity of lymphedema after nonradical surgery 2°: Quality of life, fertility outcomes and problems

SCC squamous cell cancer, *Adenoca* adenocarcinoma, *SLN* sentinel lymph nodes, *LVSI* lympho vascular space invasion

Case 3: FIGO Stage 1A2

Age, parity, PS	25 years, nulliparous, PS = 0
Co -morbidities	History of epilepsy
Screening test	Pap smear: High grade dyskaryosis on smear, HPV positive
LLETZ	Invasive squamous cell carcinoma, horizontal spread: 12 mm × 9 mm, depth of invasion: 3.3 mm. Incomplete excision at radial margins and ectocervical margins. No LVSI
Repeat LLETZ	Focal changes of CIN, no residual cancer
MRI	No residual tumour, lymph nodes normal
Surgery	Laparoscopic sentinel lymph node biopsy
Histopathology	Right pelvic sentinel lymph node: 4 tumour free lymph nodes, one tumour free left external iliac sentinel lymph node

Q. What Is the Role of Sentinel Lymph Nodes in Early Stage Cervical Cancer?

In stage IA2–IB1 (tumor size <2 cm) cervical cancer, lymph node assessment should be done in all cases as the incidence of lymph node metastasis is around 6%. Sentinel lymph node (SLN) assessment is acceptable and feasible for performing lymph node evaluation in early stage cervical cancer (stage IA2–IB1), low volume disease. The advantages of sentinel nodes include reduced morbidity like lymphocyst formation, lymphedema and reduced duration of surgery. With sentinel nodes, detection rate has also improved in unusual areas (10% cases) like presacral, common iliac, paraaortic region in which otherwise would have been missed on routine lymphadenectomy. There is also more precise histopathology evaluation of "high risk" nodes by ultrastaging for detection of macrometastasis (>2 mm), micrometastasis (0.2–2 mm) and isolated tumor cells. In cervical cancer both micro- and macro- metastasis have prognostic significance. Submitting sentinel nodes for frozen section may allow tailoring of management; if SLN is negative patient can undergo hysterectomy or if its positive patient can be given chemoradiation. On frozen section, if all type of metastases are considered, sensitivity ranged from 42.3% to 87.5% and negative predictive value ranged from 89.7% to 98% whereas sensitivity ranged from 56.4% to 88.9% and negative predictive value ranged from 91% to 98.8% if ITCs were excluded [16].

Indocyanine green preferably or combination of radiocolloid and patent blue dye are used and it is feasible to retrieve the sentinel lymph nodes laparoscopically. Sentinel nodes should be harvested from each hemiplevis. Bilateral sentinel lymph node identification is recommended and if unilateral sentinel node is identified, complete lymphadenectomy should be performed on the unmapped site. All enlarged lymph nodes should also be removed. This is followed by removal of uterus and parametrectomy [17]. The most common (90%) sentinel node pathway is the lymphatic channels crossing over the internal iliac vessels and draining into the obturator group or medial to external iliac vessels [18].

In a recent prospective observational SENTIX trial, the analysis of secondary end points results showed that bilateral detection was achieved in 91% (355/395), and it was unaffected by tumour size, tumour stage or body mass index, but it was lower in older patients, in patients who underwent open surgery, and in sites with fewer cases. Most SLN and positive SLN were localised below the common iliac artery bifurcation. Frozen sections failed to detect 54% of positive lymph nodes (pN1), including 28% of cases with macrometastases and 90% with micrometastases [19].

SLN biopsy in early stage cervical cancer has high sensitivity (96.4%) and negative predictive value (99.3%). The false negative rate is 3.6%. However, each center should audit their own data and assess their positivity rates before completely changing their practice to sentinel nodes [20]. There is a learning curve required for skill acquisition, with rigorous monitoring of surgical performances and outcomes; sentinel node biopsy should be offered as a centralized service within a cancer center.

At present not much data is present on the survival outcomes of patients who have undergone SLN assessment. In a retrospective analysis, the 2 and 5 years disease free survival in patients who underwent bilateral SLN biopsy alone and those who underwent bilateral pelvic lymphadenectomy was 97% *vs.* 95% and 93% *vs.* 92% respectively [21]. In a post-hoc analysis of both SENTICOL I and SENTICOL II cohorts presented at the ASCO 2020, the DFS patients was also similar between the two groups at 85.1% *vs.* 80.4%, P = 0.24 [22]. To date, three ongoing prospective clinical trials aim to assess the oncological outcomes of SLN biopsy in early stage cervical cancer: the SENTIX trial, the PHENIX trial and the SENTICOL III trial [16].

Case 4: FIGO Stage IB2

Age, parity, PS	50 years, P2+0, PS = 0
Co -morbidities	No comorbidities, smoker
Screening test	Pap smear: High grade dyskaryosis on smear, HPV positive
Examination	No visible growth on cervix, uterus normal size, cervix hard, flushed and high up, bilateral parametrium free Colposcopy: Suspicious of invasive cancer
LLETZ	Squamous cell cancer, grade 2, 20 mm × 10 mm × 8.5 mm (depth), possible LVSI It is present at endocervical, ectocervical and deep lateral margins Tumor stage is at least 1B1
MRI	No residual disease, no parametrial invasion and nodal enlargement
Surgery	Radical hysterectomy + ovarian conservation + bilateral pelvic lymphadenectomy Uterus normal, no visible growth on cervix, bilateral parametrium normal, bilateral obturator nodes slightly enlarged
Histopathology	Well differentiated non keratinizing squamous cell cancer 2.5 × 1.8 × 1.5 cm, LVSI +, deep stromal invasion present

Q. How Do We Perform Clinical and Radiological Assessment for Stage of Cervical Cancer? What Is the Role of Examination Under Anaesthesia?

The first step in staging is a pelvic examination. Per speculum examination is done to determine the size and location of the growth, nature (infiltrative/exophytic), and presence of vaginal extension. On vaginal examination besides confirmation of findings of speculum examination, uterine size, presence of adnexal mass and parametrial extension is determined. A rectovaginal examination is additionally done to have a more precise clinical assessment of the parametrial extension.

Examination under anesthesia (EUA) is nowadays usually not required due to high accuracy of cross sectional imaging. However, an EUA can be performed in certain situations for instance when there is a discrepancy between clinical assessment and imaging for staging or if there is a requirement of cystoscopy (in cases when there is suspicious bladder invasion on MRI) to rule out bladder involvement.

For all tumors IB1 and beyond, cross sectional imaging (MRI abdomen and pelvis) is required for staging cervical cancer. Magnetic resonance imaging (MRI) (T2 weighted) is done for assessing tumor volume, depth of stromal invasion, parametrial extension, vaginal extension and bladder and rectal involvement. The presence of an **intact hypointense stromal rim** has a high negative predictive value of almost 100% in excluding parametrial invasion. If there is vaginal involvement, the intact vaginal wall is interrupted by an intermediate signal intensity tumor. However, clinical assessment is more accurate to determine vaginal involvement compared to imaging as the latter has higher false positive rates especially in bigger tumors.

In patients planned for fertility sparing surgery MRI is used to estimate the distance of the tumor from cervical isthmus. The timing of MRI should be at least 2–3 weeks post LLETZ to avoid misinterpretation due to post procedure inflammatory changes. Ultrasound also has a good accuracy in trained expert hands [23].

While CT scan and MRI rely on anatomy and morphology to determine involvement, PET- CT has higher accuracy as it offers combined benefits of anatomic and functional imaging, and has been used to localize areas of increased FDG uptake with improved anatomic specificity. The accuracy of MRI, CT scan and PET- CT for assessing lymph node involvement is shown in Table 11.4 [24]. Diffusion weighted MRI has also been recently used to differentiate between metastatic and non metastatic lymph nodes by using tissue diffusion properties and calculation of the apparent diffusion coefficient (ADC). It is considered to be more sensitive than PET-CT scan (87% versus 66%) but was less specific (83% versus 94%).

Table 11.4 The accuracy of MRI, CT scan and PET-CT for assessing lymph node involvement

	MRI	CT scan	PET-CT
Sensitivity	0.54(0.46–0.61)	0.57 (0.44–0.69)	0.66 (0.56–0.75)
Specificity	0.93 (0.91–0.95)	0.91 (0.88–0.94)	0.97 (0.95–0.98)
Positive likelihood ratio	8.2 (6.0–11.1)	6.4 (4.4–9.4)	19.3 (12.3–30.2)
Negative likelihood ratio	0.50 (0.43–0.58)	0.47 (0.35–0.63)	0.35 (0.27–0.47)

Q. What Is the Recommended Management of IB1 Cancer Cervix?

For early cervical cancer both surgery and chemoradiation have equivalent outcomes in terms of recurrence rate and overall survival. A general principle followed in treatment of cervical cancer is to avoid multimodality treatment with both surgery and radiation as dual treatment is associated with increased morbidity without affecting the overall prognosis. Surgery should be considered as first line as the long term quality of life is better following surgery than radiotherapy. The standard management is a type C 1 radical hysterectomy or a modified radical hysterectomy (Type B) with bilateral pelvic lymphadenectomy [25]. Since radical hysterectomy with pelvic lymphadenectomy involves extensive dissection near bladder, rectum, ureters and great vessels and nerves of pelvis, this leads to higher chances of injuries to these viscera and consequent bowel injuries, ureteric injuries, neuropathies, lymphocyst and lymphedema formation. Besides these complications related to major surgeries can also occur like haemorrhage, infection, thromboembolism, pulmonary embolism, myocardial infarction, pneumonia, fluid electrolyte imbalance.

Select cases can be offered conservative surgery if the criteria of Concerv trial is fulfilled [13]. As the incidence of ovarian metastasis is less than 1% in squamous cell cancers, conservation of ovaries can be offered in younger women.

Q. Role of Minimally Invasive Surgery

In 2018, LACC, a randomized clinical trial was published comparing the disease-free survival between the laparotomic and the minimally invasive approaches' RH [26]. The 3 year disease-free survival (DFS) was lower in the MIS arm compared to the open arm (91.2% versus 97.1%; Hazard ratio 3.74) Similar findings were noted for overall survival (93.8% versus 99.0%, HR 6.00). A SEER database analysis also reported inferior outcomes with MIS compared to open surgery i.e. increase in the risk of death in 4 years in comparison to open surgery (9.1% vs. 5.3%) [27].

Recently there has been many observational studies stating that these inferior outcomes may be overcome by no vaginal manipulation, conization prior to surgery, choosing selected cases with a low-risk profile characterized by tumor size <2 cm, no LVSI, depth of invasion <10 mm, and no lymph-node involvement. However, the quality of evidence is still low and the guidelines recommend open approach of surgery [28].

Q. Adjuvant Treatment?

Further management after surgery depends on the histopathology and risk stratification. Adjuvant therapy should be considered if the final histo-pathologic findings suggest the risk of disease reoccurrence. **Sedlis criteria** defines the patients with intermediate-risk disease, which includes the presence of two of the three factors LVSI, deep cervical stromal invasion and tumour size >4 cm.

Such patient require post operative radiotherapy (PORT) without chemotherapy as in this case [29, 30].

PORT consists of whole pelvic EBRT of 45–50 Gy to cover tumor bed and draining lymph nodes. Brachytherapy boost may be considered for patients with close margins, large or deeply invasive tumours, extensive LVSI or if high risk factors are positive. Brachytherapy is delivered by ovoids or cylinders is delivered to upper one third of vagina in two weekly fractions of high dose rate (HDR) brachytherapy of 6 Gy each [25].

Recently, there have been studies comparing observation versus PORT in patients with intermediate risk factors. In a recent systematic review with meta-analysis relative risk of recurrence (RR 1.49; 95% CI 0.81, 2.75) and the relative risk of mortality (RR 1.34; 95% CI 0.71, 2.54) were similar in both groups independently whether they did or did not receive adjuvant therapy [31]. Various prospective trials are also ongoing comparing adjuvant therapy and observation [32].

High-risk disease patients include positive surgical margins or positive pelvic lymph node or parametrium spread. These patients should be offered adjuvant concurrent chemoradiation according to the survival benefit demonstrated by GOG 109 [33].

Case 5 FIGO Stage IB2

Age, performance status	47 year P1 + 0 Prev LSCS, smoker, PS = 0
Clinical presentation	C/o post coital bleeding and irregular bleeding Examination: 4 cm growth proliferative growth arising from posterior lip of cervix, uterus normal size, no vaginal involvement, bilateral parametria free not involved
Cervical biopsy	Poorly differentiated non keratinizing squamous cell cancer LVSI +
MRI:	3.3 × 3.8 cm abnormal intermediate signal mass consistent with cervical tumour. No parametrial invasion. No enlarged lymph nodes. Suspicious involvement of vagina

Q. Further Investigations

Pelvic examination and biopsy with or without colposcopy are mandatory to diagnose cervical cancer. Imaging aids to provide additional information that may impact further treatment, not used solely to stage the disease. Imaging modalities like magnetic image resonance imaging (MRI)/PET-CT/Endovaginal/transrectal ultrasound can also determine the local extension and nodal involvement and confirm the extent of spread and aid in deciding the treatment options for the patient.

Q. Management

Patients with stage IB2 are managed via Type C radical hysterectomy which includes removal of uterus en block with upper one-half of vaginal tissue, parametrium (round, broad, cardinal, uterosacral ligaments) in addition to lymph node assessment. Usually a nerve sparing type C radical hysterectomy is performed. Consent should be taken regarding morbidity and related risks, like increased intraoperative blood loss, increased blood transfusion, infections, longer operative time and operative injury to bladder, ureter, blood vessels, nerves and rectum and fistula formation. Long term morbidity includes bladder, bowel and sexual dysfunction, lymphedema and thigh pain.

Q. What Are the Prognostic Factors for Early Stage Cervical Cancer?

Major prognostic factors are stage, nodal status, number of lymph nodes, tumour volume, depth of cervical stromal invasion and lympho-vascular space invasion (LVSI). Disease stage is the most important prognostic factor followed by lymph node status. After radical hysterectomy and pelvic lymphadenectomy, patients of stage IB1 have a five-year survival rate of 91.6% compared with 60% for those with pelvic lymph node involvement [28].

Q. Recommended Follow Up for Early Stage Cervical Cancer

Objectives of follow up includes early detection of recurrent disease, assessment of quality of life, patient education of symptoms of recurrence, management of side effects, support and rehabilitation. Follow up should be individualized taking into account prognostic factors and estimated risk of relapse, primary and adjuvant treatment and short and long term side effects. Since majority of recurrences are in the first 2 years, follow up is more intensive every 4–6 months in the first 2 years and then 6–12 months upto 5 years [34].

At each visit, a detailed history should be taken regarding symptoms of recurrence like bleeding, urinary, bowel complaints and regarding long term and late effects of treatment. A pelvic examination (speculum and bimanual examination) must be done at each visit. Cervical cytology has no benefit in previously treated cervical cancers. Following radiation therapy, it is difficult to interpret the cervical cytology results. Even in group of patients who have been treated with surgery for early stage cervical cancer, cervical cytology has doubtful role in follow up apart from in women who have had fertility preserving surgery. Imaging should be performed if patient experiences symptoms suspicious of recurrence or morbidity. MRI is preferred to detect pelvic recurrence and if positive PET-CT should be performed to rule out distant metastasis [9].

Key Points

1. Early stage cervical cancer includes FIGO stages IA, IB1, IB2 and is determined by the depth of stromal invasion and overall tumour size.
2. For stage IA1 without LVSI: simple hysterectomy is definitive treatment, if family is complete and conization is preferred if future fertility is desired. For patients with positive cone margins, repeat cone or extra facial hysterectomy is done.
3. Stage IA1 with LVSI invasion and for stage IA2 modified radical hysterectomy with lymphadenectomy is preferred. For fertility preservation conization or trachelectomy is preferred. Sentinel lymph node biopsy can be done for lymph node evaluation.
4. For stages IB1 and IB2 Type C1/C2 radical hysterectomy is preferred. Open route of surgery is the recommended approach.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021:71:209–249.
2. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Mäenpää J, Andrijono A, Purwoto G, Maheshwari A, Bafna UD, Plante M, Natarajan J. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet. 2019;145(1):129–35. https://doi.org/10.1002/ijgo.12749. Epub 2019 Jan 17. Erratum in: Int J Gynaecol Obstet. 2019 Nov;147(2):279-280. PMID: 30656645.
3. Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, et al. International Endocervical Adenocarcinoma Criteria and Classification (IECC): a new Pathogenetic classification for invasive adenocarcinomas of the endocervix. Am J Surg Pathol. 2018;42(2):214–26.
4. WHO Classification of tumours. Female genital tumours. 5th ed. 2020.
5. Rutgers JK, Roma AA, Park KJ, Zaino RJ, Johnson A, Alvarado I, et al. Pattern classification of endocervical adenocarcinoma: reproducibility and review of criteria. Mod Pathol. 2016;29(9):1083–94.
6. Roma AA, Mistretta TA, Diaz De Vivar A, Park KJ, Alvarado-Cabrero I, Rasty G, et al. New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome. Gynecol Oncol. 2016;141(1):36–42.
7. Ramirez PT, Pareja R, Rendón GJ, Millan C, Frumovitz M, Schmeler KM. Management of low-risk early-stage cervical cancer: should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? Gynecol Oncol. 2014;132(1):254–9.
8. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz A, Ngan H, Pecorelli S. Carcinoma of the cervix uteri. Int J Gynaecol Obstet. 2006;95(Suppl 1):S43–S103. https://doi.org/10.1016/S0020-7292(06)60030-1. PMID: 29644676.
9. NCCN clinical practice guidelines in oncology, Cervical cancer version 1. 2023 Jan 6, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed 21 Jan 2023.
10. van Meurs H, Visser O, Buist MR, Ten Kate FJ, van der Velden J. Frequency of pelvic lymph node metastases and parametrial involvement in stage IA2 cervical cancer: a population-based study and literature review. Int J Gynecol Cancer. 2009;19(1):21–6. https://doi.org/10.1111/IGC.0b013e318197f3ef. PMID: 19258936.
11. Rogers LJ, Luesley DM. Stage IA2 cervical carcinoma: how much treatment is enough? Int J Gynecol Cancer. 2009;19(9):1620–4.
12. Fokom Domgue J, Schmeler KM. Conservative management of cervical cancer: current status and obstetrical implications. Best Pract Res Clin Obstet Gynaecol. 2019;55:79–92.

13. Schmeler KM, Pareja R, Lopez Blanco A, Humberto Fregnani J, Lopes A, Perrotta M, Tsunoda AT, Cantú-de-León DF, Ramondetta LM, Manchana T, Crotzer DR, McNally OM, Riege M, Scambia G, Carvajal JM, Di Guilmi J, Rendon GJ, Ramalingam P, Fellman BM, Coleman RL, Frumovitz M, Ramirez PT. ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer. 2021;31(10):1317–25. https://doi.org/10.1136/ijgc-2021-002921. Epub 2021 Sep 7. PMID: 34493587.
14. The SHAPE trial. http://www.gcig.igcs.org/Spring2012/2012_june_shape_trial.pdf.
15. CovensA. GOG Protocol. 278 http://www.gcig.igcs.org/Spring2012/2012_june_cervix_cancer_committee.pdf.
16. Balaya V, Guani B, Pache B, Durand YG, Bonsang-Kitzis H, Ngô C, Mathevet P, Lécuru F. Sentinel lymph node in cervical cancer: time to move forward. Chin Clin Oncol. 2021;10(2):18.
17. Cormier B, Diaz JP, Shih K, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol. 2011;122:275–80.
18. Cibula D, Abu-Rustum NR, Dusek L, et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. Gynecol Oncol. 2012;124(3):496–501.
19. Cibula D, Kocian R, Plaikner A, Jarkovsky J, Klat J, Zapardiel I, Pilka R, Torne A, Sehnal B, Ostojich M, Petiz A, Sanchez OA, Presl J, Buda A, Raspagliesi F, Kascak P, van Lonkhuijzen L, Barahona M, Minar L, Blecharz P, Pakiz M, Wydra D, Snyman LC, Zalewski K, Zorrero C, Havelka P, Redecha M, Vinnytska A, Vergote I, Tingulstad S, Michal M, Kipp B, Slama J, Marnitz S, Bajsova S, Hernandez A, Fischerova D, Nemejcova K, Kohler C. Sentinel lymph node mapping and intraoperative assessment in a prospective, international, multicentre, observational trial of patients with cervical cancer: the SENTIX trial. Eur J Cancer. 2020;137:69–80. https://doi.org/10.1016/j.ejca.2020.06.034. Epub 2020 Aug 1. PMID: 32750501.
20. Salvo G, Ramirez PT, Levenback CF, Munsell MF, Euscher ED, Soliman PT, Frumovitz M. Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. Gynecol Oncol. 2017;145(1):96–101.
21. Lennox GK, Covens A. Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer? Gynecol Oncol. 2017;144(1):16–20. https://doi.org/10.1016/j.ygyno.2016.08.337. Epub 2016 Oct 11. PMID: 27742472.
22. Balaya V, Guani B, Magaud L, et al. Ong-term oncological safety of sentinel lymph node biopsy in early-stage cervical cancer. J Clin Oncol. 2020;38:6006.
23. Fischerova D, Cibula D, Stenhova H, et al. Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer. Int J Gynecol Cancer. 2008;18:766–72.
24. Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. Gynecol Obstet Investig. 2017;82(3):209–22.
25. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021;155(Suppl 1):28–44. https://doi.org/10.1002/ijgo.13865. PMID: 34669203; PMCID: PMC9298213.
26. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med. 2018;379:1895–904.
27. Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. N Engl J Med. 2018;379:1905–14.
28. Guimarães YM, Godoy LR, Longatto-Filho A, Reis RD. Management of early-stage cervical cancer: a literature review. Cancers (Basel). 2022;14(3):575. https://doi.org/10.3390/cancers14030575. PMID: 35158843; PMCID: PMC8833411.
29. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol. 1999;73:177–83.
30. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology study. Int J Radiat Oncol Biol Phys. 2006;65:169–76.
31. Gómez-Hidalgo NR, Úrsula A, Rodríguez TG, et al. Adjuvant therapy in early-stage cervical cancer after radical hysterectomy: are we overtreating our patients? A meta-analysis. Clin Transl Oncol. 2022;24:1606.
32. Rodriguez J, Viveros-Carreño D, Pareja R. Adjuvant treatment after radical surgery for cervical cancer with intermediate risk factors: is it time for an update? Int J Gynecol Cancer. 2022;32(10):1219–26. https://doi.org/10.1136/ijgc-2022-003735. PMID: 36511890.
33. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000;18:1606–13.
34. Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol. 2017;146:3–10.

Advanced Stage Cervical Cancer

12

Anastasios Tranoulis and Beshar Allos

Introduction

Cervical cancer (CC) represents the fourth most common malignancy and fourth most common cause of malignancy-related death amongst women worldwide [1]. Approximately, two third of the women are diagnosed with locally advanced (LACC) or CC [2]. According to the revised 2018 FIGO classification for CC, LACC is defined as a cervical cancer of stage IB3-IVA, whilst advanced stage IVB includes cervical cancer with distant metastases [3].

Accurate staging is essential for the prognosis and optimal management of CC. Multidisciplinary assessment and multimodality comprehensive treatment approaches are the key to improving the outcomes. The revised FIGO 2018 staging permits the use of any of the imagining modalities depending upon the available resources, e.g. ultrasound, computed-tomography (CT), magnetic resonance imaging (MRI), or fluorine-18-labeled fluoro-2-deoxy-D-glucose positron emission tomography ([18F]FDG-PET/CT), to obtain additional information on tumour size, nodal status, parametrial invasion, and pelvic or distant metastases [3].

Concurrent platinum-based chemoradiotherapy (CCRT) is the treatment of choice for women LACC [4, 5]. For selected women with 2018 FIGO stage IB3, radical hysterectomy with or without neoadjuvant chemotherapy may also be an option with a view to minimizing the radiotherapy (RT) related genitourinary and gastrointestinal toxicity [6, 7]. To reduce the RT-induced toxicity, newer radiation techniques using intensity-modulated radiation therapy (IMRT)/volumetric arc treatment have been incorporated to the treatment of CC [8–10]. For advanced CC which stage IVB, combination chemotherapy with carboplatin/paclitaxel or cisplatin/paclitaxel is recommended [11, 12] followed by chemoradiotherapy depending upon response to initial chemotherapy. Addition of bevacizumab can also be considered [13]. Women with limited distant metastatic disease at presentation, confined to the para-aortic lymph node (stage IIIC2), treatment is administered with a curative intent with definitive extended field chemo-radiotherapy along with brachytherapy. Finally, effective involvement of palliative care team and surgical interventions including diversion stoma, ureteric or

A. Tranoulis (✉)
Department of Gynaecological Oncology, The Pan-Birmingham Gynaecological Cancer Centre, Birmingham City Hospital, Birmingham, UK
e-mail: Anastasios.tranoulis1@nhs.net

B. Allos
University Hospitals Birmingham NHS Foundation Trust, Clinical Oncology, Birmingham, UK
e-mail: b.allos@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_12

colonic stenting, and nephrostomies are always considered as appropriate for an individual case and these diversions or stentings are done to relieve symptoms, improve functions and also to reduce radiotherapy induced impact on bowel and urinary functions.

Case Scenarios

Case 1: Squamous Cell Cancer Cervix Stage 3C1

Age, Parity, PS	45 years, P4+0, PS-1
Clinical presentation	Bleeding P/V and blood mixed discharge × 6 months Defaulted from cervical cancer screening program for 10 years 5 cm growth circumferentially involving the cervix extending to posterior upper 1/3rd of vagina
Biopsy	Poorly differentiated squamous cell cancer
MRI	Cervical growth 5 × 4.5 × 6 cm extending to vagina posteriorly, bilateral parametrial invasion with moderate right sided hydronephrosis, enlarged right sided obturator node measuring 2.8 cm in short axis
PET scan	SUV max 14 in right obturator node No uptake in Para aortic nodes, diffuse uptake (SUV max 28) in cervix

Q. Discuss further Management

This is case of LACC with positive pelvic lymph nodes (PeLN) (2018 FIGO stage IIIC1r). Following discussion in the multidisciplinary team (MDT) meeting, an appropriate referral to the medical oncology team is required. Primary concurrent chemo-radiotherapy (CCRT) with weekly cisplatin concurrent with RT is the treatment of choice for women with LACC [4, 5]. The current recommended treatment approach in radical curative-intent radiotherapy of CC consists of three elements: external-beam radiotherapy (EBRT) of the primary tumour with PeLN and -if involved- para-aortic lymph nodes (PaLN) to a total dose of 45–50 Gy, brachytherapy (BT) and concomitant chemotherapy with cisplatin with weekly doses of 40 mg/m^2 [4, 5]. The old-fashioned simple opposing or 4-field box technique has been replaced by the intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT), which allow precise dose delivery and maximum dose reduction in normal tissues. Typical BT dose protocols contained 3–5 fractions with doses of 5–7 Gy each. The use of MRI for image-guided adaptive brachytherapy (IGAPT) was evaluated in EMBRACE study, which showed effective and stable local disease control across all stages of LACC, with a limited severe morbidity per organ [14].

Hydronephrosis is a common complication of LACC and is associated with a poorer prognosis [15]. Patients with LACC with suspected or confirmed hydronephrosis should always have renal function assessed and monitored and be referred for a diverting procedure urgently if feasible. Urinary diversion in cases of obstructive uropathy caused by LACC is needed to prevent deterioration of renal functions, which enables patients to tolerate cisplatin concurrent chemotherapy better and results in better oncological outcomes [16]. Urinary diversion usually involves nephrostomy unilateral or bilateral, however antegrade or retrograde stenting can be attempted in less severe ureteric obstruction. The insertion of a double-J stent and the percutaneous nephrostomy is urinary diversion options that can be offered to the patients. Insertions of double-J stents in metastatic ureteral obstruction secondary to LACC are rather challenging owing to the high rate of failures of insertions [16]. Percutaneous nephrostomy is seemingly slightly superior in restoring renal function, but can of course impact patient's quality of life, promote increasing urinary infections and patients need input from community nurses to take care of their nephrostomies [16]. Patients with renal impairment may have restrictions to receive cisplatin during chemoradiation and are at increased risk of toxicities and treatment complications when compared to patients with normal renal function [17]. For patients with impaired renal functions, despite all efforts of urinary diversions, may not tolerate cisplatin but maybe considered for weekly carboplatin [17].

Q. Evaluation of Lymph Node Metastasis in LACC: Surgical Staging Versus Radiologic Staging

Nodal metastasis, tumour volume and local extracervical spread are three major prognostic factors impacting survival in women with LACC [18]. Histological subtypes also influence prognosis. Adequate pre-treatment detection of nodal metastasis is crucial for improving treatment outcomes [18]. Pelvic and para-aortic nodal involvement is common in LACC and can be upto 30–50% and 10–25%respectively [19]. PeLNs are included routinely in CCRT fields and receive a local boost when necessary [19]. Detection of PaLN involvement is crucial, as it can result in upstaging and also subsequent modification of radiotherapy treatment planning with extended-field radiotherapy. The optimal strategy for detecting PaLN metastases in LACC remains debatable. The true-positive rate of [18F]FDG-PET/CT-assessed PaLNs is 50–100% with an overall rate of 78%. Therefore, when uptake is present in both pelvic and para-aortic regions, EBRT should be performed without PaLN dissection, as lymphadenectomy will not provide any further information. In the rare case of isolated [18F]FDG-PET/CT-positive PaLNs, surgical staging can be considered to avoid over-treatment owing to false-positive result. On the other hand, the false-negative rate of [18F]FDG-PET/CT-negative PaLN ranges between 5% and 17% with an overall rate of 12% [19]. Interestingly, only 50% of women with PET-CT false-negative PaLN have metastases <5 mm, whilst only 22% of PeLN were [18F]FDG-PET/CT-positive at the time of lymphadenectomy [19]. In a recent meta-analysis, the overall false-negative rate for detection of para-aortic nodes was11% when PeLNS were [18F]FDG-PET/CT-negative and PaLN detection was false negative in 21% when PeLNs were [18F]FDG-PET/CT-positive [19]. In latter cases, surgical staging maybe considered to improve detection rate of PaLN involvement so as to avoid under-treatment. Furthermore, if extended-field RT was routinely administered in such cases, 79% of women could be over-treated. The incidence of isolated supra-mesenteric lymphadenopathy amongst women with [18F] FDG-PET/CT-negative PaLNs who underwent laparoscopic PaLN lymphadenectomy up to the level of left renal vein, was rare [19]. Therefore, infra-mesenteric dissection seems an acceptable option to reduce overall surgical morbidity [17].

The UTERUS-11 randomised trial has compared the oncological outcomes between [18F] FDG-PET/CT- based radiological and surgical evaluation of PaLN in LACC, and demonstrated that the overall (OS) and progression-free survival (PFS) were not statistically different, whilst the cancer-specific survival favoured the surgical assessment of PaLN. Furthermore, surgical staging was safe and neither delayed CCRT nor increased complications [20].

Q. Discuss Neoadjuvant Chemotherapy Versus Surgical Debulking Prior to RT for Bulky Nodes >1.5 cm

Bulky lymph node (LN) can be defined as a LN with a short axis >1.5 cm or >2 cm on imaging; yet, a consensus on a single definition is lacking. Currently two strategies are used to treat bulky LNs: high-dose boost RT as part of standard CCRT or nodal debulking prior to CCRT [17]. Surgical excision of bulky LNs prior to CCRT may increase the chance of sterilization and decrease the risk of toxicity by omitting boosting. Some studies demonstrated effective nodal control by boosting in women with bulky LNs [21]. On the other hand, few studies showed a benefit in nodal control by surgical excision prior to RT; yet, these studies were performed before the introduction of concurrent CCRT [22]. Both strategies are associated with different types of treatment-associated toxicities (surgical morbidity versus genitourinary/gastrointestinal toxicity). A recent comparative observational study failed to demonstrate superiority of the addition of nodal boosting or debulking over CCRT for bulky LNs > 1.5 cm on oncological outcomes [23]. Until more robust evidence becomes available, nodal boosting is seemingly a better approach, as nodal debulking may potentially increase the risk of surgical toxicity as well as delayed increase risk of lymphedema compared to nodal boosting and potential delays in completion of treatment [23].

Q. Prognosis and Follow Up

Despite the advances in the management of LACC, the 5-year OS remains around 60–70%. The 5-year OS for clinical and pathological FIGO 2018 stage III is approximately 52% (53% in IIIC1, 43% in IIIC2) and 45% (71% in IIIC1, 45% in IIIC2), respectively [24, 25].

Follow-up is both for detection of disease recurrence but also for management of effects of treatments like radiotherapy and chemotherapy on patients, as well palliation of symptoms in patients with suboptimal response to treatment and have persistent on going disease. Follow ups are for assessment of physical, psychological and social wellbeing of these patients with advanced stage cervical cancer. If women have a local relapse in the pelvis then further treatment like exenterative surgery may have a place provided it is a unifocal, central pelvis recurrence. However for small lateral pelvic side wall recurrence which is not encroaching the sacrosciatic notch and its underlying sciatic nerve can be offered laterally extended endopelvic resection (LEER) with some success in surgeons versed in performing these extensive surgeries [17]. Most relapses (75%) occur within the first 2–3 years after the primary treatment, hence a closer follow up is beneficial in first 2–3 years and subsequently the follow ups can be more spaced out. Every institution has their own follow up protocol and in fact after 5 years patients can have an open ended follow up where they can seek for medical help if develop any symptoms otherwise do not need to attend for any clinical examination.

Follow up visits should include a detailed patient history, complete physical examination, with a pelvic–rectal exam. There is no definitive evidence supporting the routine use of imaging. Some women develop complete fusion of vagina following brachytherapy and hence not possible to perform a physical inspection or examination of cervix. In these situation regular MRI every 6–12 months maybe required in first 3–4 years. In some women examination under anaesthesia and release of vaginal adhesions may be needed to allow these women who are mostly young to be able to have sexual intercourse and also sometimes hydrocolpos or hematocolpos may form which may need drainage if symptomatic. In UK all women are given vaginal dilators with vaginal lubricants to use at least once a week to prevent vaginal adhesions to form over the cervix.

In women with clinical suspicion of recurrence, MRI is usually recommended and if cancer is suspected on MRI then [18F]FDG-PET/CT may be performed to confirm the recurrence. PET-CT helps in confirmation of recurrences and also assessment of location of recurrences as this will allow planning of management of these cases. PETCT has both a high sensitivity (86%) and specificity (87%) for detection of recurrences [24, 25]. If multifocal recurrence found then palliative chemotherapy may be considered. There is increasing interest of immunotherapy treatment for advanced stage cervical cancer recurrences and require analysis of PDL1 assessment in tumour tissue to identify suitable patients who may have some benefit from immunotherapy treatments which are expensive and have increasing side-effects. Biopsy is attempted where feasible to confirm diagnosis of recurrence.

Q. Implications of Revised Staging of Cervical Cancer in Tumour Prognosis

The updated 2018 FIGO classification uses imaging and pathological findings to designate the final stage of the disease. This new version has improved capacity to discriminate between the three subgroups of stage IB. Furthermore, inclusion of lymph node status is a major change that more accurately reflects the prognosis. Nevertheless, survival remains heterogeneous among patients within stage III subgroups [3].

It is important to note that patients with stage IIIC from the 2018 FIGO system would have been assigned to other groups based on the 2014 FIGO system. In the stage IIIC group from the 2018 FIGO system were most commonly assigned to stage IIB in the 2014 FIGO system, although the 2014 stages ranged broadly from IA1 to IIIB [24, 25]. In the 2018 FIGO system, stage IIIC1/IIIC2 had better survival than stage IIIA/IIIB, and stage IIIC1 had better survival than stage IIIC2 [24, 25].

Case 2: Cervical Adenocarcinoma 1B3

Age, Parity, PS	35 years, P2+0, PS-0
Clinical presentation	Post coital bleeding × 4 months regular smears Examination: Growth 5 × cm arising from the endocervix, bilateral parametria free
Biopsy	Moderately differentiated adeno carcinoma
MRI	MRI: Cervical mass 5 cm with ballooning of endocervical canal, no extracervical extension, no parametrial extension
PET scan	FDG uptake in cervical mass (SUV max 19.2) with no evidence of metabolically active disease outside the cervix

Q. Discuss Further Management

Stage 1B3 adenocarcinoma management is always a topic of debate as it has been managed in so many different ways across different centres. Standard accepted treatment is concurrent chemoradiotherapy involving external beam radiotherapy (IMRT) with Cisplatin followed by vaginal brachytherapy [17]. [18F]FDG-PET/CT is recommended prior to commencing treatment to exclude any lymphatic involvement. Some centres do surgical assessment of PaLN assessment to assess the field of external beam radiotherapy required for these cases.

The ongoing OUTBACK and INTERLACE trials have been conducted to ascertain any benefits of additional adjuvant chemotherapy after concurrent CCRT and the role of induction chemotherapy plus CCRT as first-line treatment for LACC, respectively [26, 27]. In the OUTBACK trial, there was no evidence of survival difference between treatment groups (OS at 5 years ACT versus control: 72% vs 71%). The PFS at 5 years was also similar in those assigned ACT versus control (63% vs 61%). The anti-CTLA-4 checkpoint inhibitor ipilimumab and PD-1 inhibitor pembrolizumab can also be considered [28].

Radical surgery is an alternative option in certain histological subtypes like clear cell cancer which are poor responders to radiotherapy and invariably require adjuvant surgery for persistent disease and surgery becomes more complex after pelvic irradiation. Similarly adenocarcinoma of cervix also have an inferior sensitivity to radiation compared to squamous cell ca. Survival after surgery and CCRT is similar in both the groups for stage1B3 cervical cancers. However adjuvant chemoradiotherapy is recommended in presence of single major histological risk factors which are (1) narrow (<5 mm) or involved excision margins, (2) positive metastatic pelvic nodes or (3) parametrial extension, or presence of combined intermediate risk factors, which are deep stromal invasion, extensive LVSI and large tumour size (Delgado score). A randomized trial from Europe did not see any statistically significant survival difference between radiotherapy versus surgical treatment for stage 1B3 cervical cancer. Other studies have also shown benefit of surgical treatment for this stage of cervical cancer for younger patients to prevent radiotherapy impact on vaginal functions. There is also another approach of shrinking stage 1B3 cervical cancer with neoadjuvant chemotherapy prior to surgery and reduce need for double treatment. Randomised trial by Landoni did show a higher morbidity after double treatment than with radical surgery or radiotherapy alone especially urinary complications, lymphedema and gastrointestinal morbidity. However several adaptations in adjuvant treatment like mobilizing omentum as tissue spacers in pelvis reduces bowel and urinary morbidity if adjuvant radiotherapy was required after surgery in cases with adverse histological factors. Similarly radiotherapy fields are modified to small field in absence of pelvic nodal involvement and if margins are clear then brachytherapy is avoided. Hence double treatment though conventionally regarded as increasing morbidity proves beneficial in certain selected group of these patients.

If surgical management is being undertaken then LN assessment should be performed as the first step of surgical management. All sentinel lymph nodes (SLN) from both sides of the pelvis and/or any suspicious LNs should be sent for the frozen section. Should intraoperative SLN assessment be negative or not done, systematic PeLN dissection should be performed. Querleu-Morrow type C2 radical hysterectomy and bilateral PeLN

dissection is recommended, should the frozen section of SLNB be negative. If LN involvement is detected intra-operatively including macro-metastases (>2 mm) or micro-metastases (0.2–2 mm), further PeLN dissection and radical hysterectomy should be avoided. Patients should be referred for definitive CCRT. PALND, at least up to inferior mesenteric artery, may be considered for staging purposes [6, 17].

Neoadjuvant chemotherapy (NACT) followed by radical surgery is a controversial alternative. Although it is not associated with improved oncological outcomes in LACC and might lead in trimodal treatment, it might have a role in the subgroup of 2018 FIGO stage IB3 cervical cancer [7].

Q. Discuss Role and Benefits of Neoadjuvant Chemotherapy (NACT)

NACT followed by radical surgery is a controversial alternative, as there is no robust evidence to support the benefit of tumour downsizing with regards to prognosis and systemic treatment toxicity. A randomised trial by Gupta et al., demonstrated that the 5-year disease-free survival was significantly lower in the NACT + surgery than in CCRT arm (69.3% *versus* 76.7%), whilst the corresponding 5-year OS rates were similar (75.4% *versus* 74.7%) [29]. Approximately 30% of the patients in NACT arm, required CCRT owing to failure of treatment. The rates of rectal toxicity (5.7% *versus* 13.3%), bladder toxicity (2.8% *versus* 7.3%) and vaginal toxicity (19.9% *versus* 36.9%) at 90 days after treatment were significantly lower in the NACT arm, whilst 24 months after treatment there was no difference in rectal and bladder toxicities between the two groups and vaginal toxicity continued to be lower in the NACT arm (12.0% *versus* 25.6%).

The most recent EORTC trial demonstrated similar results in the crude analysis. Specifically, the 5-year PFS was 56.9% in NACT arm and 65.6% in CCRT arm, whilst the corresponding 5-year OS rates were 61.8% versus 67.7% [7]. Nonetheless, in subgroup analysis, the NACT arm showed a trend to better 5-year OS in patients with stage IB3 disease (82% *versus* 76%). Short-term grade 3–4 adverse events occurred more frequently in NACT arm (41% *versus* 22%), whilst grade 3–4 chronic toxicities were more frequent in CCRT arm (21% *versus* 15%). This evidence suggest that NACT followed by radical hysterectomy may have a role in FIGO stage IB3 CC, as it may lead to similar or improved oncological outcomes compared to primary CCRT, by reducing at the same time the treatment-associated toxicity.

Q: Surgical Modifications to Improve Morbidity from Radiotherapy

Ovarian transposition (OT) is an effective strategy amongst pre-menopausal women, undergoing pelvic RT to minimise ovarian exposure and damage, and therefore, prevent early menopause. One or both ovaries are separated from the uterus and mobilised away from the area where the RT will be administered. Ovaries may be transposed more than 1.5 cm above the iliac crest, usually at the level of lower kidney pole to ensure minimal irradiation. Ovarian transposition could be performed on young patients (<40 years) with tumors smaller than 4 cm, and it should be avoided in those with bulky tumors. Ovarian function preservation after ovarian transposition and pelvic RT, with or without chemotherapy can be achieved in approximately 60% of the cases [30]. It is associated with low risk of surgical complications, ovarian cyst formation and ovarian metastasis [30]. The reported risk of ovarian metastasis is 0.5% and it is associated with bulky tumours [30].

The close proximity of the cervix to the bladder, rectum and vagina leads to radiation-induced genitourinary and gastrointestinal toxicities, which hinder the delivery of curative doses to the tumour. To overcome this limitation, an omental spacer can be surgically placed in the pelvis between the tumour and gastrointestinal tract. This can be performed laparoscopically before primary CCRT or during laparotomy following radical hysterectomy or NACT and radical hysterectomy, as there is a chance for adjuvant RT considering the high-risk features of stage IB3 CC. Although there is a substantial body of evidence for the use of spacers in other types of malignancy [31], there is currently a paucity of

data in CC, deriving almost exclusively from case series on the use of spacers prior to re-irradiation for recurrent CC [32].

Q. Discuss Biologic Behaviour of Adenocarcinoma Versus Squamous Cell Carcinoma and Their Response to Treatment

Clinical characteristics and prognosis of cervical adenocarcinoma (ADC) differ from SCC. Women with ADC have been reported to be younger and more often Caucasian, diagnosed at early-stage and more likely to have metastatic LNs [33]. Moreover, ADC is associated with poorer prognosis compared to SCC, especially in LACC, and characterised by higher resistance to RT and higher chemoresistance compared to SCC [33].

Q. Prognosis and Follow Up

The 5-year OS and PFS in 2018 FIGO stage IB3 cervical cancer is approximately 90% and 89%, respectively [24, 25].

International guidelines recommend follow-up evaluation every 3–4 months for the first 2 years and every 6 months for the next 3 years. Patients should return to annual population-based general physical and pelvic examinations after 5 years. Follow-up visits should include a complete physical examination, with a pelvic–rectal exam and a detailed patient history [17]. Self-reporting of symptoms like vaginal or rectal bleeding/discharge, abdominal or pelvic pain, loss of weight, backache, bladder or bowel habits alterations and leg oedema should alert the responsible clinician for possible recurrence. There is no definitive evidence supporting the routine use of imaging, nonetheless, the later should be performed in case of suspected recurrence. MRI pelvis and CT abdomen/thorax are useful imaging modalities to ruling out local or distal metastasis, whilst [18F]FDG-PET/CT is usually a useful imaging adjunct for the assessment of local, nodal and distal disease [17]. Biopsy should be taken when possible to confirm diagnosis [17].

Case 3: Squamous Cell Cancer Cervix Stage IVa

Age, Parity, PS	55 years, P3+0, PS-0
Clinical presentation	Blood stained vaginal discharge × 1 year Continuous dribbling of urine × 4 months Not regular with smears Examination: Exophytic growth 6 cm from cervix involving anterior vaginal wall. Clear urinary leak + 1 cm vesico vaginal fistula felt above the growth bilateral parametria involved up to lateral pelvic wall
Biopsy	Moderately differentiated squamous cell carcinoma

Q. Describe Further Work Up and Management

This is a case of histologically confirmed grade 2 SCC. In light of the lateral side pelvic wall involvement, this is a clinical 2018 FIGO stage IIIB SCC. Nonetheless, due to the presence of anterior vaginal wall involvement and vesico-vaginal fistula, the likelihood of bladder involvement is high (clinical 2018 FIGO stage IVA SCC). A referral to the relevant MDT is required to direct further management. For histologically confirmed CC, investigations are directed towards assessment of tumour volume, vaginal or parametrial invasion, local or distal metastasis [17]. MRI pelvis and CT abdomen/thorax are required for radiological staging, whilst [18F]FDG-PET/CT is usually a useful imaging adjunct for the assessment of local, nodal and distal disease [17]. Examination under anaesthesia and cystoscopy with or without colonoscopy can also be performed to obtain biopsies from the bladder, should it be involved. Referral to the medical oncology team is required for primary chemotherapy [17]. In view of the bilateral side pelvic wall involvement (possible bilateral hydronephrosis) and the presence of vesico-vaginal fistula, a thorough assessment of renal function and referral for urinary diversion with bilateral percutaneous nephrostomies should be done prior to chemotherapy is also required [15–17].

Q. What Are the Different Chemotherapy Regimens, Rationale and Response Rates

Primary CCRT with weekly cisplatin concurrent with RT or pelvic exenteration are the treatment options for women with 2018 FIGO stage IVA [11, 12, 17]. Although vesico-vaginal and/or recto-vaginal fistulas are a common post-radiotherapy complication amongst women with stage IVA disease, these may also occur at the time of diagnosis, rendering the treatment management rather challenging.

In carefully selected group of patients, primary treatment with chemotherapy maybe followed by surgical treatment with pelvic exenteration in stage IVA CC complicated by a fistula, as these patients are not ideal candidates for primary RT. Should the patient be deemed not eligible for an exenterative procedure, palliative chemotherapy is an alternative treatment option. Carboplatin or cisplatin/paclitaxel are the preferred regimens in the first-line treatment [11, 12, 17]. For women with renal impairment who are suboptimal candidates for cisplatin, weekly carboplatin dosed by area under the curve two (AUC2) should be considered [11, 12, 17]. Urinary diversion may lead to improvement of renal function and restore suitability for cisplatin [15–17]. Bilateral percutaneous nephrostomies are also required prior to chemotherapy [15–17]. Alternative chemotherapy regimens of cisplatin and vinorelbine, cisplatin and topotecan, and cisplatin and gemcitabine have been found to be non-superior to cisplatin and paclitaxel [12]. In light of the vesico-vaginal fistula and the high risk of recto-vaginal fistula formation, addition of bevacizumab should be administered with caution. The anti-CTLA-4 checkpoint inhibitor ipilimumab and PD-1 inhibitor pembrolizumab can also be considered, especially amongst women with positive PeLN and/or PaLN [28]. Recently, a phase III study on persistent, progressive, or metastatic CC demonstrated that the addition of pembrolizumab to a first-line platinum-based regimen with or without bevacizumab provides OS and PFS benefits in women whose tumour expresses programmed death ligand-1(PDL-1) [34].

In women with stage IVA CC, the recurrence rate is high and patient survival is poor [24, 25, 35]. The poor prognosis of patients with stage IVA disease results from the high incidence of distant failure as well as poor local control. Local recurrence is the most common cause of failure after RT [24, 25, 35]. The reported local control in stage IVA CC following RT or concomitant CCRT is 39–61% [24, 25, 35]. Distant metastasis after treatment is also a failure pattern found commonly in patients with stage IVA cancer with reported rates up to 75% [24, 35]. The presence of pre-treatment hydronephrosis and vesico-vaginal/recto-vaginal fistulas are reported to be significant variables for poorer survival in women with stage IVA CC after definitive RT [15, 16, 35]. Palliative chemotherapy can achieve acceptable response rates which, however, are only partial and of short duration. The median OS of patients who undergo palliative chemotherapy for LACC or recurrent CC ranges between 8 and 11 months [36].

Q. Discuss Exenteration Versus Urinary Diversion Followed by Chemoradiation

In women with histologically confirmed stage IVA CC, exenteration may be an alternative to primary CCRT, should the PeLN and PaLN be negative and the presence of distal metastasis be ruled out. Although vesico-vaginal and/or recto-vaginal fistula formation is a well-recognized complication of RT, occasionally these may occur at diagnosis, rendering the treatment planning challenging. In such cases, an exenterative procedure is the treatment of choice. This may involve performing infra-or trans-levator ani total, posterior or anterior exenteration [37–40]. The most important negative prognostic factors in women undergoing exenterations are tumor-involved PeLD/PaLN, fixation of the tumour to the pelvic side wall and tumour-involved resection margins in the surgical specimen [37]. In this case, in view of the bilateral lateral involvement of the pelvic side wall, a curative exenterative procedure is not possible, however, in highly selected women, laterally extended endopelvic resection (LEER) is an alternative option [40]. Nonetheless, this

procedure is associated with extremely high morbidity/mortality and poor quality of life [37–40]. Compete resection of the disease is of utmost importance, as the 5-year OS in case R0 is approximately 50 vis-a-vis 0% for an R1 resection, respectively [37–40]. Palliative exenterative procedure or sole urinary diversion e.g. ileal conduit formation, followed by CCRT is an alternative option to chemotherapy. Nonetheless, the pelvic radiation-associated morbidity should also be thoroughly discussed with the patients. As this major surgery is associated with a high morbidity, palliative versus curative indication must be thoroughly assessed, and women ought to be counseled extensively prior to surgery. The role of NACT prior to exenterative procedure to improving oncological outcomes remains vague [41].

Case 4: Squamous Cell Cancer Cervix Stage IVB

Age, Parity, PS	60 years, P1+0, PS-2
Clinical presentation	Foul smelling blood stained vaginal discharge × 2 years Breathlessness × 6 months Had regular smears till 45 years after that defaulter Examination: Exophytic growth 5 cm from cervix, right parametria involved upto lateral pelvic wall, left parametrium medial half involved
Cervical biopsy	Moderately differentiated squamous cell carcinoma
MRI	Cervical growth 5 × 6 cm with bilateral parametrial involvement and extending to lower uterine segment
X ray chest	Multiple cavitating lesions in the right lung with pleural effusion Same confirmed on CECT chest
MRI brain	Normal
PET CT	FDG avid cervical growth. FDG avid lesions in right lung (4–5) 0.5–1 cm, a small 1 cm FDG avid lytic lesion in the L1 spine? Malignant

Q. Benefits of PET CT in Stage IVB Disease

Use of ([18F]FDG-PET/CT) improves initial staging by providing information on extra-pelvic and para-aortic sites, such as supra-clavicular and mediastinal LNs, lung, bone, peritoneum, omentum, adrenal gland, and liver [42, 43]. ([18F] FDG-PET/CT) has proved more accurate than high-resolution CT alone, particularly in showing the presence of regional LN involvement and extra-pelvic disease extension [42, 43]. It has a sensitivity of 100%, specificity of 90%, and accuracy of 94% for evaluating distant disease in CC [42, 43].

Q. Further Management

In medically fit women with distant metastatic disease at presentation, combination chemotherapy is recommended [17]. Carboplatin or cisplatin/paclitaxel are the preferred regimens in the first-line treatment [11, 12, 17]. Addition of bevacizumab to standard chemotherapy is recommended in women with good performance status and where the risk of significant gastrointestinal/genitourinary toxicity has been carefully assessed and discussed with the women [13, 17]. Spine magnetic resonance imaging is required for evaluating the avid L1 spinal lesion. Palliative RT may be considered to alleviate severe pain and decrease the likelihood of spinal cord compression. A dose of 20 Gy in 5 fractions over a week or 30 Gy in 10 fractions over 2 weeks is commonly advocated [44]. Immune checkpoint inhibitors targeting both the PD-L1 and CTLA-4 axes can also been considered [28].

Q. Prognosis

The survival amongst women with 2018 FIGO stage IVB is rather poor. The 5-year OS ranges from 0% to 44%, and approximately 50% of the reported deaths occur within 1 year from diagnosis [45].

Case 5: Cervical Cancer with Ovarian Metastasis

Age, Parity, PS	47 years, P5+0, PS-1
Clinical presentation	Presented to emergency with acute abdominal pain and distension × 2 days bilateral masses in ovary with ascites on ultrasound. Provisional diagnosis: Bilateral ruptured ovarian cysts, mucinous content and ascites Underwent diagnostic laparoscopy followed by staging laparotomy, Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omental biopsy and appendicectomy Intra-operative findings: Bilateral ruptured ovarian cysts each 10 cm. Three litres of mucinous ascites. Peritoneum inflamed. Normal appendix. Normal uterus. Normal omentum, diaphragm, Morrison's pouch, stomach and splee
Co morbidities	Nil
Histopathology	Primary endocervical adenocarcinoma, usual type, grade 1, 30 mm × 8.2 mm superficial 1/3rd stromal invasion, closest margin 1.2 cm, no vaginal involvement, invasion into lower uterine segment, myometrium normal Bilateral ovarian and fallopian tube serosal metastasis Parametrium free of tumour, omental biopsy and appendix negative PAX 8, CK7, CEA, CA125 positive, p16 block positive, p53- wild type CK2, CK20, CDX2, WT1, ER, PR negative. Cervical and ovarian tumor have same immunoprofile, s/o metastatic endocervical adenocarcinoma Cytology: Ascitic fluid showed no malignant cells

Q. Incidence of Ovarian Metastasis in Cervical Cancer

Ovarian metastases in CC are rather low with adenocarcinomas (ADC) being more likely to metastasize to the ovaries than SCCs. The overall incidence of ovarian metastases (OM) in CC (2018 FIGO stage IA-IIB) is approximately 3.5% in ADC and 1.5% SCC, respectively [46]. The risk of OM is seemingly higher in women with older age (>40 years), bulky tumours, nodal metastasis, lymphovascular involvement, parametrial invasion or corpus uteri invention [46].

Q. Management

This is an incidental finding of CC with OM a laparotomy in the emergency setting for ruptured bilateral ovarian cysts. A referral to the gynaecological oncology multidisciplinary team meeting is required. An MRI pelvis and CT abdomen/thorax supplemented by a PET-CT is required to evaluate the parametrial and nodal status as to rule out the presence of local or distal metastasis. Although OM would not change her International Federation of Gynecology and Obstetrics (FIGO) stage (provisionally IB2), based on FIGO 2018 staging, it would impact on the patient's prognosis. In the absence of OM, the management of CC identified in a type A hysterectomy includes either a laparotomy for parametrectomy, vaginectomy, and bilateral PeLN to avoid adjuvant CCRT in the presence or intermediate/high risk factors (LVSI, deep stromal invasion, tumour size >4 cm, parametrial, vaginal or nodal involvement) or primary CCRT [17]. In this case, the pathological analysis showed a grade 1 ADC with low risk factors; notwithstanding, owing to the unknown parametrial and nodal status and in view of the OM, definite CCRT is the management of choice [41]. Due to the rarity of OM in CC and the incidental finding of CC in a type A hysterectomy, the evidence concerning the optimal management of such cases is rather scarce.

Q. Explain the Prognosis and Follow Up

The outcome for patients with CC and OM is very poor, indicating that OM is the cardinal prognostic factor [47]. The 5-year survival rate for women with OM is approximately 45% in stage IB, 38% in stage IIA, and 18% in stage IIB, respectively [48]. Interestingly, risk factors, such as histology, FIGO stage, and LN involvement, are seemingly not significant in CC with OM [48]. Surveillance of metastatic spread is also challenged in view of the rare nature of this presentation and lack of supporting data. While metastatic adenocarcinoma in situ of the cervix to the ovary is rare, additional sites of metastasis, such as pulmonary lesions, have been reported [49].

Close monitoring with regular clinical examination on a 3 monthly basis. In order to detect metastatic spread, such as pulmonary deposits, imaging in the form of CT thorax/abdomen/pelvis on an annual basis for 3 years is recommended.

Key Points

1. Accurate staging is essential for the prognosis and optimal management of cervical cancer.
2. Multidisciplinary assessment and multimodality comprehensive treatment approaches are the key to improving the outcomes.
3. The revised FIGO 2018 staging permits the use of any of the imagining modalities depending upon the available resources. ([18F]FDG-PET/CT) is a reliable imaging modality for obtaining information on nodal status, parametrial invasion, and pelvic or distant metastases
4. Concomitant chemoradiotherapy is the treatment of choice in locally advanced cervical cancer.
5. For highly selected patients radical hysterectomy with or without neoadjuvant chemotherapy may be an alternative option for 2018 FIGO stage IB3.
6. In case of severe hydronephrosis or vesicovaginal fistula, a thorough assessment of renal function and referral for urinary diversion with bilateral percutaneous nephrostomies should be done prior to chemoradiotherapy.
7. Ovarian metastases in cervical cancer is uncommon. However, ovarian metastasis is seen more with adenocarcinoma histology than squamous cell carcinomas of the cervix.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
2. Shrivastava S, Mahantshetty U, Engineer R, et al. Treatment and outcome in cancer cervix patients treated between 1979 and 1994: a single institutional experience. J Cancer Res Ther. 2013;9:672–9.
3. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018;143(Suppl 2):22–36.
4. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2001;358:781–6.
5. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer–a meta-analysis. Clin Oncol (R Coll Radiol). 2002;14:203–12.
6. Cibula D, Abu-Rustum NR, Fischerova D, Pather S, Lavigne K, Slama J, Alektiar K, Ming-Yin L, Kocian R, Germanova A, Frühauf F, Dostalek L, Dusek L, Narayan K. Surgical treatment of "intermediate risk" lymph node negative cervical cancer patients without adjuvant radiotherapy-A retrospective cohort study and review of the literature. Gynecol Oncol. 2018;151(3):438–43.
7. Kenter G, Greggi S, Vergote I, Katsaros D, Kobierski J, Massuger L, van Doorn HC, et al. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994. J Clin Oncol. 2019;37:abstr. 5503.
8. Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, Manigandan D, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. Int J Radiat Oncol Biol Phys. 2013;87:542–8.
9. Marnitz S, Lukarski D, Köhler C, Wlodarczyk W, Ebert A, Budach V, Schneider A, Stromberger C. Helical tomotherapy versus conventional intensity-modulated radiation therapy for primary chemoradiation in cervical cancer patients: an intraindividual comparison. Int J Radiat Oncol Biol Phys. 2011;81:424–30.
10. Lim K, Small W Jr, Portelance L, Creutzberg C, Jürgenliemk- Schulz IM, Mundt A, Mell LK, et al. Gyn IMRT consortium: consensus guidelines for delineation of clinical target volume for inten-sity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys. 2011;79:348–55.
11. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gyneco-logic Oncology Group study. J Clin Oncol. 2004;22:3113–9.
12. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27:4649–55.
13. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gyneco-logic Oncology Group 240). Lancet. 2017;390:1654–63.

14. Pötter R, Tanderup K, Schmid MP, Jürgenliemk-Schulz I, Haie-Meder C, Fokdal LU, Sturdza AE, et al. EMBRACE Collaborative Group MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol. 2021;22(4):538–47.
15. Pradham TS, Duan H, Katsoulakis E, et al. Hydronephrosis as a prognostic indicator of survival in advanced cervix cancer. Int J Gynecol Cancer. 2011;21:1091–6.
16. New FJ, Deverill SJ, Somani BK. Outcomes related to percutaneous nephrostomies (PCN) in malignancy-associated ureteric obstruction: a systematic review of the literature. J Clin Med. 2021;10(11):2354.
17. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie-Meder C, Köhler C, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer. Virchows Arch. 2018;472(6):919–36.
18. Gouy S, Seebacher V, Chargari C, Terroir M, Grimaldi S, Ilenko A, Maulard A, Genestie C, Leary A, Pautier P, Morice P, Deandreis D. False negative rate at 18F-FDG PET/CT in para-aortic lymphnode involvement in patients with locally advanced cervical cancer: impact of PET technology. BMC Cancer. 2021;21(1):135.
19. Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. Gynecol Obstet Investig. 2017;82(3):209–22.
20. Marnitz S, Tsunoda AT, Martus P, Vieira M, Affonso Junior RJ, Nunes J, Budach V, Hertel H, Mustea A, Sehouli J, Scharf JP, Ulrich U, Ebert A, Piwonski I, Kohler C. Surgical versus clinical staging prior to primary chemoradiation in patients with cervical cancer FIGO stages IIB-IVA: oncologic results of a prospective randomized international multicenter (Uterus-11) intergroup study. Int J Gynecol Cancer. 2020;30(12):1855–61.
21. Gogineni E, Bloom B, Diaz Molina F, et al. Radiotherapy dose escalation on pelvic lymph node control in patients with cervical cancer. Int J Gynecol Cancer. 2021;31:524–9.
22. Cosin JA, Fowler JM, Chen MD, et al. Pretreatment surgical staging of patients with cervical carcinoma: the case for lymph node debulking. Cancer. 1998;82:2241–8.
23. Olthof EP, Wenzel H, van der Velden J, Spijkerboer AM, Bekkers R, Beltman JJ, Nijman HW, Slangen B, Smolders R, van Trommel N, Zusterzeel PLM, Zweemer R, Stalpers LJA, van der Aa M, Mom C. Treatment of bulky lymph nodes in locally advanced cervical cancer: boosting versus debulking. Int J Gynecol Cancer. 2022;32(7):861–8. https://doi.org/10.1136/ijgc-2022-003357.
24. Wright JD, Matsuo K, Huang Y, et al. Prognostic performance of the 2018 International Federation of Gynecology and Obstetrics Cervical Cancer Staging Guidelines. Obstet Gynecol. 2019;134(1):49–57.
25. Yan DD, Tang Q, Chen JH, Tu YQ, Lv XJ. Prognostic value of the 2018 FIGO staging system for cervical cancer patients with surgical risk factors. Cancer Manag Res. 2019;11:5473–80.
26. Mileshkin LR, Moore KN, Barnes E, Gebski V, Narayan K, Bradshaw N, Monk BJ. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: the randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). J Clin Oncol. 2021;39(Suppl. S18):LBA3. https://doi.org/10.1200/JCO.2021.39.15_suppl.LBA3.
27. National Cancer Institute. Clinical trials home page. https://clinicaltrials.gov/ct2/show/NCT01566240.
28. Duranti S, Pietragalla A, Daniele G, Nero C, Ciccarone F, Scambia G, Lorusso D. Role of immune checkpoint inhibitors in cervical cancer: from preclinical to clinical data. Cancers (Basel). 2021;13(9):2089.
29. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri Chopra S, Kerkar R, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage Ib2, IIa, or IIb squamous cervical cancer: a randomized con-trolled trial. J Clin Oncol. 2018;36:1548–55.
30. Buonomo B, Multinu F, Casarin J, Betella I, Zanagnolo V, Aletti G, Peccatori F. Ovarian transposition in patients with cervical cancer prior to pelvic radiotherapy: a systematic review. Int J Gynecol Cancer. 2021;31(3):360–70.
31. Kawaguchi H, Demizu Y, Mukumoto N, Ishihara T, Miyawaki D, Komatsu S, Akasaka H, Shinoto M, Shioyama Y, Nakamura K, Fukumoto T, Sasaki R. Efficacy of spacers in radiation therapy for locally advanced pancreatic cancer: a planning study. Anticancer Res. 2021;41(1):503–8.
32. Barcellini A, Mirandola A, Fiore MR, Orlandi E, Cobianchi L. Omentum flap as a spacer before carbon ion radiotherapy for gynecological recurrences. A technical note. Cancer Radiother. 2022;26(4):599–603.
33. Hu K, Wang W, Liu X, Meng Q, Zhang F. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma of cervix after definitive radiotherapy or concurrent chemoradiotherapy. Radiat Oncol. 2018;13(1):249.
34. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385:1856–67.
35. Hata M, Koike I, Miyagi E, Numazaki R, Asai-Sato M, Kaizu H, Mukai Y, Takano S, Ito E, Sugiura M, Inoue T. Radiation therapy for stage IVA uterine cervical cancer: treatment outcomes including prognostic factors and risk of vesicovaginal and rectovaginal fistulas. Oncotarget. 2017;8(68):112855–66.

36. Tambaro R, Scambia G, DiMaio M, Pisano C, Barletta E, Iaffaioli VR, Pignata S. The role of chemotherapy in locally advanced, metastatic and recurrent cervical cancer. Crit Rev Oncol/Hematol. 2004;52:33–44.
37. Marnitz S, Köhler C, Müller M, Behrens K, Hasenbein K, Schneider A. Indications for primary and secondary exenterations in patients with cervical cancer. Gynecol Oncol. 2006;103(3):1023–30. https://doi.org/10.1016/j.ygyno.2006.06.027. Epub 2006 Aug 4. PMID: 16890276.
38. Ungar L, Palfalvi L, Novak Z. Primary pelvic exenteration in cervical cancer patients. Gynecol Oncol. 2008;111(2 Suppl):S9–12.
39. Numa F, Ogata H, Suminami Y, Tsunaga N, Nakamura Y, Tamura H, et al. Pelvic exenteration for the treatment of gynecological malignancies. Arch Gynecol Obstet. 1997;259:133–8.
40. Höckel M. Laterally extended endopelvic resection (LEER) – principles and practice. Gynecol Oncol. 2008;111:S13–7.
41. Lopez-Graniel C, Dolores R, Cetina L, Gonzales A, Cantu D, Chanona J, et al. Pre-exenterative chemotherapy, a novel approach for patients with persistent or recurrent cervical cancer. BMC Cancer. 2005;5:118.
42. Liu FY, Yen TC, Chen MY, et al. Detection of hematogenous bone metastasis in cervical cancer: 18F-fluorodeoxyglucose-positron emission tomography versus computed tomography and magnetic resonance imaging. Cancer. 2009;115(23):5470–80.
43. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. Gynecol Oncol. 2007;106(1):29–34.
44. Sharma DN, Gandhi AK, Adhikari N. Definitive radiation therapy of locally advanced cervical cancer initially treated with palliative hypofractionated radiation therapy. Int J Radiat Oncol Biol Phys. 2016;96:E306.
45. Lea JS, Sheets EE, Wenham RM, Duska LR, Coloman RL, Miller DS, Schorge JO. Stage IIB-IVB cervical adeno-carcinoma: prognostic factors and survival. Gynecol Oncol. 2002;84:115–9.
46. Fan Y, Wang MY, Mu Y, Mo SP, Zheng A, Li JK. Ovarian metastasis in women with cervical carcinoma in stages IA to IIB: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(31):e21146.
47. Turashvili G, Farmer P, Colgan T, Childs T. Human papillomavirus-related ovarian metastasis with Endocervical adenocarcinoma: report of 2 cases and review of literature. J Low Genit Tract Dis. 2015;19(4):e60–3.
48. Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol. 2006;101:234–7.
49. Horn L-C, Höhn AK, Stark S, et al. Endocervical adenocarcinoma in situ (AIS) with ovarian and pulmonary involvement: report of a case and review of the literature suggesting a “seed and soil hypothesis”. J Cancer Res Clin Oncol. 2019;145:2061–9.

13 Incompletely Treated and Recurrent Cervical Cancer

Kavita Singh and Bindiya Gupta

Introduction

Surgery and chemoradiotherapy are the standards of treatment for cervical cancers. Choice of treatment is dependent upon stage, histological type, menopausal status, and tumour size and location. Surgery is beneficial for early stage cervical cancer but also has a role to play in selected cases of locally advanced cervical cancer where the chemoradiotherapy has not been administered in full doses, or in cases who have persistent disease after complete administration of chemoradiotherapy for locally advanced stage cervical cancer. There are clinical situations where the cervical cancer was unsuspected and was an incidental finding on final histology and completion surgery may be required for getting adequacy of margins and also for exclusion of any regional metastasis in pelvic nodes. Surgery is also required in certain locoregional recurrence of cervical cancer. This chapter will be discussing different types and effectiveness of salvage surgery in all these various clinical scenarios.

Case 1: Incompletely Operated Cancer Cervix

Age, PS	48 years, P2+0, ECOG −0
Clinical presentation	C/O: Intermenstrual bleeding/ postcoital bleeding with high grade dyskaryosis smear Backache × 3 months Previous 2 LLETZ for high grade CIN 5 and 7 years ago Chronic smoker Examination: Cervical ectopy +
Co morbidities	Nil
Transvaginal sonography	Endometrial thickness: 16 mm; bilateral polycystic ovaries
Colposcopy endometrial biopsy	High grade changes with flushed cervix, HPV +ve and Type 3 transformation zone. Cervical punch biopsy revealed CIN3, further LLETZ not feasible in view of short cervix flushed with vault Endometrial biopsy: Normal menstrual endometrium
Colposcopy MDT	Recurrent CIN3 with short cervix flushed with vaginal vault—recommended simple hysterectomy
Surgery	Total laparoscopic hysterectomy + salpingectomy for persistent CIN
Histology	CIN 3, with associated single foci of well differentiated squamous cell cancer 3 mm wide × 5 mm deep × 7 mm length, LVSI positive and extending to ectocervical margin, tubes free of tumor

K. Singh (✉)
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_13

Q. Further Investigations

Histology revealed an incidental finding of invasive well differentiated squamous cell cancer of cervix which was not suspected preoperatively. Histologically this cancer is at least stage 1B1 with LVSI positive with involved ectocervical margins. This patient needs careful discussion in a multidisciplinary meeting with a central path review to confirm the findings and presence of LVSI. In case the report is adenocarcinoma additional findings to be discussed in MDT are to identify Silva pattern of invasion to assess risk of lymphatic metastasis and recurrence. Silva pattern is subdivided into 3 categories: Tumors with a nondestructive pattern of invasion (pattern A) are associated with a 0% rate of lymph node metastases, whereas focally (B) and diffusely (C) destructive patterns have 4% and 23% rates of nodal involvement, respectively (Table 13.1) [1]. Similarly, pattern A tumors had 0% recurrence and 0% fatality rates, compared with pattern B tumors (1.2% and 0%, respectively) and pattern C tumors (22.1% and 8.8%, respectively) [2].

This patient did have risk factors of predisposing to development of cervical cancer and these were recurrent high grade smear abnormality, symptoms of recurrent post coital bleeding, chronic smoker and type 3 transformation zone. Clinical examination is crucial and colposcopy assessment may not be adequate because of type 3 transformation zone and punch biopsy of cervix does not necessarily reveal complete assessment of cervix. Based on histology this patient has Stage 1B1 squamous cell cancer (SCC) of cervix associated with risk factors of involved excision margins with cancer and presence of lymphovascular space invasion. Traditionally the treatment for stage 1B1 SCC of cervix is radical hysterectomy with pelvic lymph node assessment. In perimenopausal women bilateral oophorectomies are also discussed though not mandatory for treatment of early stage SCC of cervix. As this cervical cancer is inadequately treated which is unfavourable and further treatment would therefore be essential.

Table 13.1 Tumor classification based on pattern of stromal invasion in adenocarcinoma (Pattern based classification, Silva system)

Pattern A	• Well demarcated glands with rounded contours, frequently forming groups • No destructive stromal invasion • No single cells or cell detachment • No lymphovascular invasion • Complex intraglandular growth acceptable (i.e. cribriform, papillae) • Lack of solid growth (i.e. architecturally well to moderately differentiated) • Depth of tumor or relationship to large cervical vessels not relevant
Pattern B	• Localized (limited, early) destructive stromal invasion arising from pattern A glands (well demarcated glands) • Individual or small groups of tumor cells, separated from the rounded gland, often in a focally desmoplastic or inflamed stroma • Foci may be single, multiple or linear at base of tumor • With or without lymphovascular invasion • Lack of solid growth (i.e. architecturally well to moderately differentiated)
Pattern C	• Diffuse destructive invasion, characterized by diffusely infiltrative glands with associated extensive desmoplastic response • Glands often angulated or with canalicular pattern, with interspersed open glands • Confluent growth filling a 4× field (5 mm): Glands, papillae (stroma only within papillae) or mucin lakes • Solid (architecturally poorly differentiated); nuclear grade is disregarded • With or without lymphovascular invasion

Before embarking on further treatment radiological assessment is essential to exclude any regional and distant metastasis. Contrast enhanced (diffusion weighted) MRI assessment is standard imaging performed in stage 1B1 cervical cancer. However MRI will have its limitations in distinguishing postoperative inflammatory changes and sometimes reactive nodes secondary to postoperative changes may appear enlarged and suspicious. Similarly parametrium may appear thickened and difficult to distinguish inflammatory changes from neoplasia. PET CT may be used to exclude distant metastasis and in pelvis PETCT may also be falsely positive secondary to inflammatory changes.

Q. Further Management

This patient has at least 1B1 SCC of cervix where the standard management in young patient with no comorbidities is radical hysterectomy+pelvic lymphnode assessment. This patient having had simple hysterectomy, there is a role for further staging surgery as there is cancer reaching the excision margins and completeness of excision cannot be accurately ascertained. Three surgical procedures for completion surgery will be evaluated (1) pelvic lymphadenectomy (2) parameterectomy (3) vaginal cuff excision for margins.

1. **Pelvic node assessment** preferable by laparoscopy is definitely warranted to exclude nodal metastasis and also to define the field of radiotherapy if it was considered as adjuvant treatment. If there is no pelvic nodal metastasis seen then patient can be spared external field pelvic radiotherapy which is associated with high morbidity like lower leg lymphedema, bladder and bowel complications.
2. **Role and approach to parameterectomy**: there is more evidence growing about favouring omission of parameterectomy for low volume (<2 cm) size cervical cancer. Outcome of CONCERV trial for low risk cervical cancer with tumour size <2 cm and depth of invasion <10 mm and no associated risk factors can be spared parameterectomy with a recurrence rate of 3.5% and lymph node metastasis of 5% [3].Therefore there is a case for omitting parameterectomy. Outcome of Canadian randomised controlled trial - Radical Versus Simple Hysterectomy and Pelvic Node Dissection With Low-risk Early Stage Cervical Cancer (SHAPE) trial is still awaited [4].
3. **Vaginal cuff excision for margins.** Margins following a laparoscopic hysterectomy are difficult to ascertain because of the diathermy effect and histologically it gives a misinterpretation of involved margins. Nevertheless exclusion of involvement of vaginal margins is crucial in this case as it decides whether any adjuvant chemoradiotherapy is required. Laparoscopic excision of vaginal cuff is feasible though is associated with possibility of surgical morbidity like ureteric and bladder injury secondary to recent surgical inflammation.

If there is no residual disease detected in pelvic nodes and vaginal cuff then it is safe to avoid any adjuvant radiotherapy. However in presence of residual disease or nodal metastasis then chemotherapy + chemoradiotherapy maybe required.

Role of adjuvant chemoradiotherapy always remains though it is associated with radiation induced morbidity in a young premenopausal woman and therefore is less favoured approach rather than further completion surgery.

Q. Prognosis

If this patient has a true stage 1B1 SCC of cervix then has over 95% of cure rate. However if the cancer is upstaged following surgery with detection of residual disease in the vault or in the pelvic nodes then further adjuvant treatment is required with chemoradiotherapy.

Case 2: Persistent Disease After Chemo Radiation

Age, PS	83 years, P6+0, ECOG −1
Clinical presentation	Presented for routine follow up after treatment Stage 3A squamous cell cancer cervix treated with chemoradiation (radical radiotherapy to the pelvis phase 1:45 Gy in 25 fractions over 5 weeks with IMRT, phase 2: 5.4 Gy in 3 fractions, phase 3: Intrauterine brachytherapy 21Gy in 3 fractions) completed 10 weeks back MRI image of the tumour (Fig. 13.1a)
Co morbidities	History of knee replacement, hypertension, acid reflux disease
MRI	1X 0.9 × 1.5 cm residual posterior cervical lip lesion extending to endocervix, hematometra present. No abnormalities in the vagina. No significant pelvic lymphadenopathy (Fig. 13.1b)

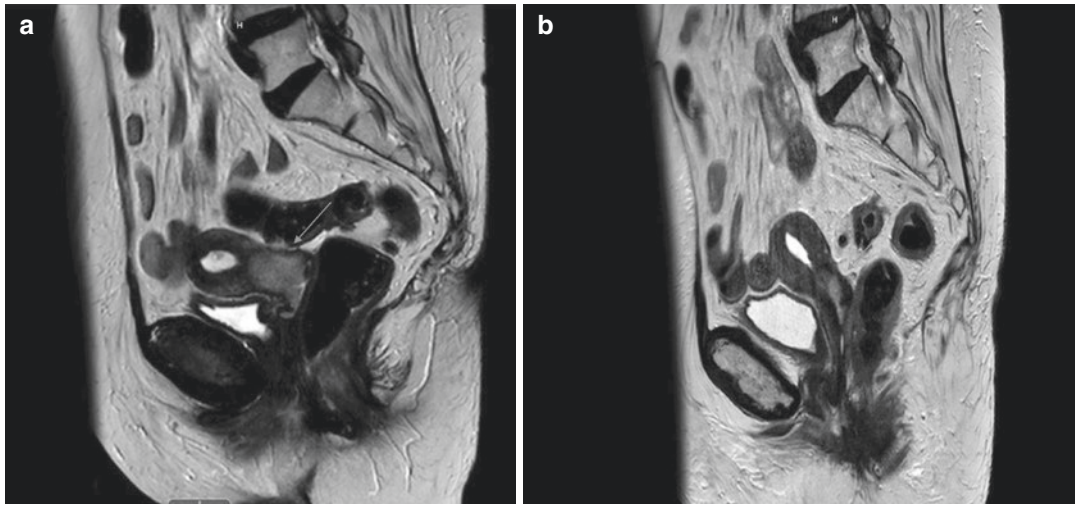


Fig.13.1 (**a**) MRI of pelvis before radiotherapy (T2 weighted image, sagittal view): 2.7 × 1.6 × 2.4 cm cervical tumor (Arrow) with right parametrial involvement and invasion of the upper vagina. The tumour was extending to the middle third of the vagina. Proximal collection in endometrial cavity. (**b**) MRI of pelvis post radiotherapy (T2 weighted image, sagittal view): Shows cervical tumour has reduced in size with a residual mass predominantly involving the posterior lip, the lesion measures around 1 × 0.9 × 1.5 cm (blue arrow), The lesion remains of intermediate signal intensity with hypoenhancement and restriction in diffusion. Small amount of fluid noted within the endometrial cavity previously

Examination under anaesthesia	Vulva and vagina normal, with fibrotic tissue as post radiotherapy—introitus tight, admitting 1 finger only, indurated tissue present Endocervical biopsy and biopsies from anterior and posterior cervical lips taken
Histology	Invasive squamous cell cancer

Q. How to Assess Response to Treatment

This is a complex case as she is elderly postmenopausal women with significant medical comorbidities with locally advanced stage SCC of cervix. She received radical dose of radiotherapy of >80 Gy and clinically it is difficult to assess for any residual disease because of vaginal stenosis. MRI done 8–12 post radiotherapy helps in evaluation for any residual cancer. Radiotherapy continues to have response in the tissues until 12 weeks post treatment. It is difficult to distinguish between persistent disease from radiation effect. This patient had a suspicious small area on posterior lip of cervix (1 × 0.9 × 1.5 cm). MRI findings for recurrent disease has a sensitivity of 77.8% and specificity of 41.7% [5]. Timing of MRI is crucial for follow up. PETCT similarly has its limitation to distinguish radiation induced inflammatory changes from residual diseases.

If in doubt examination under anaesthesia + cervical biopsy may be recommended but this also has its limitations because of sampling error and difficulty in diagnosing residual disease high in the endocervical canal or in presence of vaginal stenosis as in above case. Clinical examination difficult to distinguish radiotherapy changes and persistent disease. Cervical sampling has to be of adequate and large size to exclude persistent diasease. Electric Loop biopsy yield 31% detection of persistent disease vs 15% with forceps biopsy [5].

Q. Discuss Causes of Persistent Disease

There are several causes of persistent disease after chemoradiotherapy treatment and these are poor morphological characteristics of tumour, where the tumour size may be bulky and endophytic with extension of cancer in lower uterine segment where they maybe a failure to deliver optimum radiotherapy dose [6].

Secondly there may be a difficulty in administration of radiotherapy dose especially in presence of uterovaginal prolapse or in presence of extreme vaginal stenosis where intravaginal administration of brachytherapy may prove difficult. Thirdly, of course, there is a suboptimal response to chemoradiotherapy treatment.

Q. Discuss Indications of Salvage Surgery

Salvage surgery is a completion surgery done following **suboptimal response** to chemoradiotherapy resulting in persistent low volume residual disease in cervix. Secondly salvage surgery is also offered in cases where there is **suboptimal delivery** of chemoradiotherapy treatment which usually happens if there is poor patient compliance or tolerability or failure to deliver brachytherapy in following situations:

- selectron perforation
- failure to dilate cervix
- uterovaginal prolapse
- unable to deliver adequate dose due to restriction from organs at risk e.g. Severe diverticular disease

Management Plan

Management of persistent disease is usually surgical excision. Type of surgery is dependent upon tumour location and size of residual disease. If confined within the cervix and is low volume then a simple hysterectomy with bilateral salpingo-oopherectomy may suffice. However, if the persistent disease is involving the vaginal wall or the parametrium or pelvic side wall then exenterative surgery maybe required. In this case the patient underwent salvage hysterectomy, margins negative for disease.

Q. Prognosis

Prognosis is different where salvage surgery is performed following completion of radical dose of radiotherpapy versus salvage surgery for residual disease following incomplete/interruptions in chemoradiotherapy treatment. In persistent disease following complete administration of chemoradiotherapy, the outcome is poorer and surgical morbidity higher compared to where there has been difficulty in completing the total chemoradiotherapy administration. There is a 50% survival if the R0 (negative margins) is obtained with salvage surgery for persistent disease and is nearly 100% for second group with incomplete chemoradiotherapy [7].

Case 3: Incomplete Treatment Following Chemoradiation: Selectron Perforation

Age, PS	38 years, P4+0, ECOG −1
Clinical presentation	C/O: Vaginal discharge Stage 2B adenocarcinoma cancer cervix treated with chemoradiation (radical radiotherapy to the pelvis:45 Gy in 28 fractions over 5 weeks; had selectron perforation in first fraction of intrauterine brachytherapy MRI: 5 cm tumour in the posterior lip of the cervix, extending into the right parametrium and right adnexal region
Co morbidities	Nil
MRI (abdomen and pelvis) 6 weeks post radiotherapy	2 cm residual growth seen on posterior lip of cervix. No lymphadenopathy suggestive of good partial response
Clinical examination	Normal lax vagina, posterior lip of cervix thickened with a small 2 cm growth, (consistent with MRI findings), uterus normal size, retroverted and mobile

Q. Causes of Selectron Perforation

Selectron perforation is not common but can occur if there is stenosed cervix secondary to presence of the cervical mass or in presence of uterovaginal prolapse or in presence of any distorted anatomy due to presence of fibroids etc. In above case of a parous woman with retroverted uterus with lax vagina and cervical growth with radiotherapy fibrosis may have caused the selectron perforation.

Q. Further Management

If there has been sufficient response to EBRT which makes the cervical cancer size reduced to be confined to cervix only, then salvage hysterectomy maybe performed. Usually histologically confirmation is not required in patients who have not received full dose of chemoradiotherapy and MRI shows partial response.

In clinical situations, where the shrinkage of the cervical mass has not been adequate with 45 Gy of external beam radiotherapy and patients have persistent parametrial disease and are not appropriate for salvage hysterectomy alone or are medically not fit for surgery then further pelvic radiotherapy boost of upto 21 Gy may be given. If however in spite of the further pelvic boost, there is still persistent of cervical tumour extending into the parametrium, then careful consideration for exenterative surgery should be taken in a multidisciplinary environment.

Q. Prognosis

If there has been good response to external beam radiotherapy with only minimal /low volume residual disease then salvage hysterectomy can be curative [7]. Persistent disease after chemoradiotherapy has a grimmer outlook as it establishes radio-resistance and also the surgery required is more extensive like exenterative procedure.

Case 4: Recurrent Cancer Cervix: Nodal Recurrence Post Chemoradiation

Age, PS	58 years, P2+0, ECOG −0
Clinical presentation	C/O: Backache × 3 months Dysuria × 3 months History of chemoradiation for squamous cell cancer cervix stage 2B 3 years back Examination: Vaginal fibrosis +, no obvious growth on cervix
Co morbidities	Nil
CECT abdomen and pelvis	Multiple enlarged enhancing lymph nodes conglomerate mass 4.2 × 3.5 cm in Para aortic region compression on the left ureter with proximal left hydronephrosis.
PET CT scan	FDG avid Para aortic nodal mass SUV max 10.5

Q. Further Management

Treatment for recurrent cervical cancer is challenging and is mainly palliative. Above patient was treated with chemoradiotherapy and the radiotherapy field usually extends to pelvic and common iliac nodes. As the para-aortic nodal mass lies outside the field of previously irradiated field then re-challenge with radiotherapy is an option, though it is difficult to sterilize >4 cm nodal mass with radiotherapy alone. It will be useful to offer surgical resection of this nodal mass which will decompress the hydroureter and en-bloc resection of para-aortic nodes will be useful and preferably avoid breaching the surface

capsule of the nodal mass. To improve outcome irradiation of the para-aortic may be recommended.

Prior to embarking on radiotherapy or surgical resection, PET-CT is essential to exclude any distant metastasis.

In presence of multisite recurrences if detected then non -surgical palliative treatment is recommended which consists of chemotherapy in combination with the anti-VEGF antibody bevacizumab. Immune mechanisms are impaired in cervical cancer because of viral aetiology and therefore immunotherapy using checkpoint inhibitors seems a way forward. All recurrent or metastatic cervical cancer will benefit from assessment of PD-L1 and antiPD1 antibody pembrolizumab may be recommended in cases of recurrent cervical cancer which have progressed on other lines of chemotherapy. Another anti-PD1 antibody cemiplimab has a role in recurrent cervical cancer either alone or in combination with radiotherapy.

Other checkpoint inhibitors including nivolumab, durvalumab, atezolizumab, and camrelizumab are in different stages of clinical development for the disease. Finally, an additional targeted approach being pursued involves PARP inhibitors (rucaparib and olaparib are both in Phase II) based on earlier study results [8].

Q. Prognosis

Prognosis for recurrent cervical cancer is grim. A GOG 240 trial reported usefulness of adding bevacizumab to the chemotherapy, the ORR was improved from 36% to 48% (9), and the OS could be prolonged from 13 to 17 months for recurrent, persistent, metastatic cervical cancer, thus laying the foundation for the first-line choice of combining bevacizumab with chemotherapy for this population [9].There was however a high rate of genitourinary fistula formation with addition of bevacizumab of 15% [10].

Ongoing trial to assess efficacy of PD-1/PDL-1 inhibitors in recurrent, metastatic and advanced stage cervical cancers are underway.

Case 5: Recurrent Cancer Cervix: Post Surgery

Age, PS	38 years, P1+0, ECOG −0
Clinical presentation	C/O: Post coital bleeding one episode Previous radical hysterectomy + bilateral pelvic lymphadenectomy with ovarian conservation for stage 1b1 well differentiated adeno carcinoma cervix 4.5 years ago; no adjuvant treatment received Examination: Friable growth 2 × 3 cm at the vault, thickening of medial half of left parametrium
Co morbidities	Nil, chronic smoker
Contrast enhanced MRI Abdomen and pelvis	2.5 × 2 cm lesion at the vault with parametrium involvement on left side. Complex lesion in left adnexa 3 cm with contrast enhancement. Planes with rectosigmoid and bladder are preserved. No significant pelvic lymphadenopathy.
Biopsy from growth	Adeno carcinoma

Q. Further Management

This patient with previously treated early stage adenocarcinoma of the cervix with radical hysterectomy and pelvic lymphadenectomy has 2 sites of disease recurrence on vaginal vault and left adnexa. Adenocarcinomas of cervix have a higher incidence of metastasis to ovaries compared to squamous cell cancer of the cervix. PET-CT is required to assess for any distant metastasis. PLD-1 assessment will be useful to assess the benefit of any immunotherapy.

Options of treatment in absence of any distant metastasis is either chemoradiotherapy or further surgery. Adenocarcinoma of cervix is less radiosensitive than it squamous counterpart [11]. PET-CT excludes any other site of metastasis then surgery maybe a favoured option and will involve total pelvic exenteration with removal of bilateral residual ovaries.

If complete resection is achieved, then no further adjuvant treatment is required. However in presence of ovarian metastasis then further adjuvant with chemotherapy with or without bevacizumab maybe beneficial. Immunotherapy maybe considered if cervical cancer is PLD-1 positive. In the KEYNOTE 826 trial progression-free and overall survival were significantly longer with pembrolizumab than with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab. This was in cases of all patients with a PDL1expression combined positive score (CPS) of >1 h. Overall survival at 24 months was 53.0% in the pembrolizumab group and 41.7% in the placebo group (hazard ratio for death, 0.64; 95% CI, 0.50 to 0.81; P < 0.001) [12].

Q. Prognosis

Outcome of recurrent cervical cancer is always guarded. Survival can be 50% at 5 years for complete resection. Morbidity of exenteration is high.

Key Points

1. There is a role for completion surgery in incidentally diagnosed and incompletely operated cervical cancers
2. Salvage surgery has a role for locally advanced cervical cancer previously treated with chemoradiotherapy.
3. There is no benefit of routine practice of adjuvant hysterectomy after chemoradiotherapy for LACC
4. Salvage surgery does have a role in cases of incomplete administration of chemoradiotherapy or persistent disease after completion of chemoradiotherapy treatment.
5. Recurrent cervical cancer needs PDL-1 assessment as there is a possible favourable role of immunotherapy

References

1. Diaz De Vivar A, Roma AA, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, et al. Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. Int J Gynecol Pathol. 2013;32(6):592–601.
2. Roma AA, Diaz De Vivar A, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Teramoto N, Ali-Fehmi R, Rutgers JK, Barbuto D, Silva EG. Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. Am J Surg Pathol. 2015;39(5):667–72.
3. Schmeler KM, Pareja R, Lopez Blanco A, Humberto Fregnani J, Lopes A, Perrotta M, et al. ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer. 2021;31(10):1317–25.
4. Radical versus simple hysterectomy and pelvic node dissection with low-risk early stage cervical cancer (SHAPE). Available at: https://clinicaltrials.gov/ct2/show/NCT01658930. Accessed 18 Jan 2023.
5. Hequet D, Marchand E, Place V, Fourchotte V, De La Rochefordière A, Dridi S, Coutant C, Lecuru F, Bats AS, Koskas M, Bretel JJ, Bricou A, Delpech Y, Barranger E. Evaluation and impact of residual disease in locally advanced cervical cancer after concurrent chemoradiation therapy: results of a multicenter study. Eur J Surg Oncol. 2013;39(12):1428–34.
6. Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1994;29(1):9–16.
7. Walji N, Chue AL, Yap C, Rogers LJ, El-Modir A, Chan KK, Singh K, Fernando IN. Is there a role for adjuvant hysterectomy after suboptimal concurrent chemoradiation in cervical carcinoma? Clin Oncol (R Coll Radiol). 2010;22(2):140–6.
8. Cohen AC, Roane BM, Leath CA 3rd. Novel therapeutics for recurrent cervical cancer: moving towards personalized therapy. Drugs. 2020;80:217–27.
9. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, Monk BJ. Improved sur-

vival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734–43. Erratum in: N Engl J Med. 2017;377(7):702.

10. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, Birrer MJ, Waggoner SE, Moore DH, Look KY, Koh WJ, Monk BJ. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017;390(10103):1654–63.
11. Landoni F, Colombo A, Milani R, Placa F, Zanagnolo V, Mangioni C. Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update. J Gynecol Oncol. 2017;28(3):e34.
12. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ, KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385(20):1856–67.

14 Rare Histology: Clear Cell Cancer, Mucinous, Mesonephric Duct Cancer

Bindiya Gupta and Kavita Singh

Introduction

Persistent HPV infection is the main etiology of cervical cancer and its precursor lesions. However, in 5–10% cases cervical cancer may be HPV independent which have a different molecular profile and clinical outcome [1, 2]. The non HPV associated adenocarcinomas (NHPVA) include gastric type adenocarcinoma, clear cell type, mesonephric and endometrioid adenocarcinoma [3]. HPV independent cervical cancer may be a true negative cancer or may be due to failure to detect HPV by standard diagnostic tests, different viral genotypes, metastatic tumours or due to loss of genome during integration process [4]. These tumours are characterized by absence of p16 and presence of mutations in p53, KRAS, ARID 1A and PTEN. These tumours are associated with higher incidence of lymph node involvement, more distant metastasis and worst oncologic outcomes compared to HPV dependent cervical cancer. Till now, the management strategies are same for both HPV dependent and independent tumours, although NHPVA adenocarcinomas have variable responses to standard treatment.

B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

In this chapter we are going to discuss three clinical scenarios of HPV independent cervical cancer and their management.

Case 1: Mesonephric Duct Cancer of Cervix

Age, Parity, PS	58 years, P2+0 ECOG 1, BMI <30
Clinical presentation	Right iliac fossa pain and chronic diarrhoea **Examination**: 5 cm polypoidal mass arising from cervix extruding into the vagina with parametrial thickening on right side
Co morbidities	Nil
Cervical biopsy	Low grade spindle cell sarcoma Central pathology review: Mesonephric carcinoma with lymphovascular invasion
MRI	7 cm tumour in the posterior lip of the cervix, extending into the uterine myometrium and right adnexal region causing right hydroureter and mild hydronephrosis
CT (thorax, abdomen and pelvis)	7 cm heterogeneous pelvic mass, presence of right hydroureter and mild hydronephrosis, multiple tiny omental and pelvic peritoneal nodules. There were bilateral pulmonary nodules suspicious of metastatic disease
PET CT	Suggestive of cervical carcinoma with peritoneal spread. Lung nodules non avid

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_14

Tumour markers	CA125: 24, CA19-9: 59, CEA: 12
Treatment	**She received 6 cycles of neoadjuvant chemotherapy (carboplatin + paclitaxel)** **Post chemotherapy:** Partial response, disease confined to pelvis
Surgery	Laterally extended endopelvic resection (LEER) procedure with radical hysterectomy and bilateral salpingo oophorectomy with recto-sigmoid resection with end colostomy (Hartmann's procedure) and partial resection of the lower right ureter (6–7 cm defect) with bilateral pelvic node dissection, ureteric reimplantation using Boari flap
Intraoperative findings	Uterus normal size, 5 × 5 cm tumour in right parametrium, invading rectosigmoid and right terminal ureter 4 cm, obliterated pouch of Douglas Normal appearance of bilateral tubes and ovaries, peritoneal surfaces, liver, diaphragm, appendix and small-bowel
Histology	Mesonephric duct cancer with involvement of the rectosigmoid, right ovary and pelvic lymph nodes. Disease within a millimetre from the inked margin lateral to the right ureter, not involving the ureteric wall FIGO 2018 stage 3c1 cervical mesonephric carcinoma

Q. What Are Unique Clinical Features of Mesonephric Duct Cancers?

Mesonephric duct vestigial remnants can be seen in up to 20% of adults and are located close to the ovary (oophoron, para oophoron), in the broad ligament, lateral parts of cervix and vagina [5]. These may present as inclusion cysts, mesonephric hyperplasia or rarely mesonephric cancer. Since the ductal remnants are present deep in the lateral portion of cervix, infiltrative pattern of growth results in a barrel shaped cervix. Confluent growth results in extension into lower uterine segment, adjacent unilateral parametrial extension and these may also present as unilateral pelvic masses.

These tumours are rarely detected on screening and present in advanced stages. Due to the location of the tumour, they are usually not diagnosed on Pap smear and since these are not associated with HPV and HPV DNA testing is also negative. The diagnosis is made on cervical biopsy, cone specimens or post hysterectomy. There can be a co existing endometrioid adenocarcinoma.

Q. What Are Unique Pathological Features of Mesonephric Duct Cancer?

The unique feature on histology is that they exhibit a mixture of morphologic patterns occasionally associated with spindle cell component in 20% of the cases which may be either homologous or heterologous (Malignant mixed mesonephric tumours). It may also be associated with mesonephric hyperplasia in the background. Ki-67 is a useful marker to distinguish between hyperplasia and cancer. There is positive staining of CD10, CK7 and Calretinin with negative CEA. There may be associated positivity of Vimentin and EMA. In the present case also initially there was a spindle cell component on histopathology and on review it was proven to be a mesonephric duct cancer.

Q. What Is the Prognosis of These Tumours?

These are non-HPV related high grade adenocarcinomas and are known to be aggressive tumours [6].For stage I tumours, recurrence rate is around 32 to 33% compared to 11% in squamous cell carcinoma and 16% for adenocarcinomas [7, 8].

Q. What Is the Management for Mesonephric Duct Cancer?

Due to rarity of presentation, the true biological behaviour of these tumours is largely unknown and it is reasonable to manage these patients as cervical adenocarcinoma of similar stage.

This patient presented with stage IV disease, hence chemotherapy was started initially to reduce the tumour size and to take care of the systemic disease. There was partial response to chemotherapy and as she was developing bowel obstruction and ureteric compression, it was decided to proceed for radical pelvic surgery for the persistent disease.

Q. What Are the Types of Pelvic Exenteration?

Pelvic exenteration involves radical excision of the uterus in conjunction with the adjacent viscera from the urologic or rectal compartments. It is referred to as anterior exenteration when bladder is removed and posterior exenteration when there is associated removal of rectosigmoid. When surgical excision extends to all the three compartments i.e. bladder, uterus and rectum it is referred to as total pelvic exenteration.

Exenteration involving total removal of vagina extends below the levator ani muscle is referred to as the infra levator or trans levator exenteration. This involves complete excision of anal canal and the perineal body. In cases when lower vagina, perineal body and anal canal is not removed, it is called as supralevator exenteration as it does not include the excision of levator muscles.

The aim of surgery is to achieve clear excision margins. The success of surgery depends on the excision margins status. If there is no microscopic disease at the margins it is called as complete microscopic clearance or R0 excision and the exenteration is performed with a curative intent. When there is macroscopic clearance only it is call R1 excision and when margins are involved both microscopically and macroscopically it is called R2 excision. The latter is performed with a palliative intent, in cases when there is a malignant fistula or impending bowel obstruction.

In this case the tumour was very close to the margins and it can be labelled as R0/R1 excision.

Q. What Is Laterally Extended Endo Pelvic Resection (LEER)?

The concept of LEER was introduced by Michael Hockel on the basis that there is definite compartmentalization in female pelvis which is defined by embryonic development and theses serve as natural barriers to tumour spread. Advanced tumours transgress compartmental borders and spread within multiple compartments while recurrent disease tends to grow multi compartmental as the barriers are destroyed by previous treatment.

The aim of LEER is to resect en bloc multiple visceral compartments in the pelvis. In this procedure, exenteration (anterior, posterior or total) is laterally extended and includes excision of any of the pelvic parietal structures in the en bloc specimen like endopelvic part of the obturator internus muscle, coccygeus, iliococcygeus, and pubococcygeus to achieve a wider tumor-free margin. Occasionally internal iliac vessels may need to be excised.

The main criteria for surgery is to achieve R0 resection of the tumour, benefit the patient in terms of cure or at least prolongation of life. LEER is not indicated if the tumor involves the lumbosacral plexus or sciatic nerve (diagnosed clinically or on MRI) as it may not be able to achieve complete clearance of tumour.

Q. How Should We Select Cases for Pelvic Exenteration?

Exenterations should only be offered to well motivated patients who understand the surgical morbidity and consequences of the procedure on their quality of life. The indication in this case was persistent residual disease after partial resolution post chemotherapy.

Leg pain, lymphoedema, hydroureteronephrosis were initially regarded as an absolute contraindication of exenteration as its signified involvement of nerves, lymphatics and lateral pelvic sidewall extension. Presently, with the practice of lateral pelvic sidewall excision of tumour (Hockel's

LEER procedure), unilateral hydro ureteronephrosis is not regarded as an absolute contraindication. In the present case also there was involvement of the distal ureter, and a LEER procedure was done to completely excise the tumour and obtain free margins with ureteric reimplantation.

Case 1: Adjuvant Treatment: Chemo Radiation

Follow up: No evidence of recurrence at 2 years; NM Renogram: Normal renogram curve indicating free drainage.

Case 2: Clear Cell Cancer Cervix

Age, Parity, PS	32 years, Nulliparous ECOG 0, BMI 27
Clinical presentation	C/O blood stained vaginal discharge, foul smelling, post coital bleeding × 6 months Loss of appetite, constipation M/H: h/o prolonged cycles 2–3/2–3 months × 5 years Pelvic examination: 7 × 6 cm soft friable mass arising from cervix, post fornix thickened POD puckered, no nodularity, b/l fornix free, uterus R/V exact size could not be made out. Right parametrium minimal thickening, left parametrium free. Rectovaginal septum free
Co morbidities	Nil
Cervical biopsy	High grade adeno carcinoma favouring clear cell cancer
MRI	Heterogeneous enhancing mass 6 × 7 cm seen in cervix extending into the lower uterine segment, no parametrial extension. Bilateral adnexa normal. No retroperitoneal lymphadenopathy Stage 1B3

Q. What Are Unique Features of Cervical Clear Cell Cancer (CCC)?

It is an HPV independent neoplasm and on immunohistochemistry it is, HNF 1 beta and Napsin A positive; ER, PR p16 negative [9]. On histopathology, it consists of a papillary, tubule cystic and/or solid architecture with a clear to vacuolated glycogen rich cytoplasm and atypical nuclei. In a retrospective analysis of 58 cases of cervical clear cell cancer, 70% cases were stage 1, Silva C pattern of invasion present in 77.6%, LVSI was present in 31%, lymph node metastasis in 24%, 10.3% had distant abdomino pelvic metastasis at the time of diagnosis [10].

It has a bimodal age distribution, in women with DES exposure in utero the peak age at onset is 17–36 years while in non DES exposure CCC the second peak is much later at around 44–70 years. It may co relate with presence of genitourinary malformations like double uterus, unilateral renal agenesis etc.

Q. What Are the Management Options? What Are the Prognostic Factors?

It is similar to standard treatment protocol of cervical adenocarcinoma.

This case was stage 1B3 and was planned for chemoradiation. Since the patient was nulliparous she was also referred to an infertility specialist for fertility preservation strategies like oocyte cryopreservation. However, the patient declined for the same.

The unfavourable prognostic factors are larger tumor size, higher stage, high mitotic rate, positive margins, lymphnodes and parametrial disease [11].

Case 3: Gastric Type Adenocarcinoma Cervix

Age, Parity, PS	52 years, P3L3, BMI 33.7
Clinical presentation	Chief complaints: Post coital bleeding and foul smelling vaginal discharge × 1 year Not compliant with cervical cancer screening P/V: 2 × 3 cm soft friable mass arising from post lip of cervix (Fig. 14.1), bilateral fornix full uterus R/V exact size could not be made out. Right parametrium normal, left parametrium free minimal thickening. Rectovaginal septum free

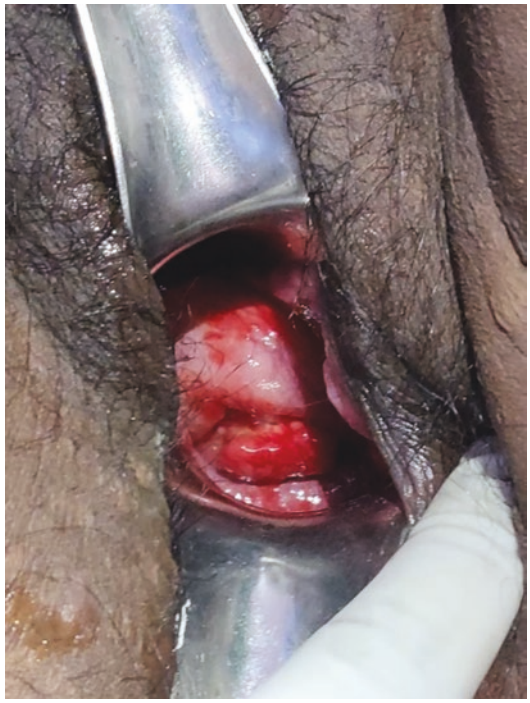


Fig. 14.1 2 × 3 cm exophytic on cervix posterior lip, anterior lip also shows erosion and hemorrhagic areas. Cervix was hard and irregular

Co morbidities	Nil
Cervical biopsy	Moderately differentiated mucinous adenocarcinoma with equivocal immunohistochemistry profile (positive for CK7, CDX 2, CEA, CK 19, PAX 8; negative for CK20). Origin is likely of upper gastrointestinal tract or pancreatic or biliary tract, but gynaecological primary is not completely ruled out
PET CT	PET CT scan showed extensive disease; avid adnexal masses; peritoneal nodularity; large omental cake and hepatic surface disease in the right subphrenic space
Endoscopy	Normal oesophagus/stomach/first and second part of duodenum Colonoscopy normal
Tumour markers	CA125: 136, CA19-9: 59, CEA: 12
Surgery	MDT discussion: Planned for surgery. Primary debulking surgery resulting in complete macroscopic clearance (R0): Modified posterior exenteration with pelvic peritonectomy, total colectomy with end ileostomy, bilateral parietal and Morrison's pouch peritonectomy, bilateral diaphragm peritonectomy and partial resection and primary closure, cholecystectomy, pyloric antrectomy and Roux en Y reconstruction, total omentectomy, splenectomy, resection of pancreatic tail disease, resection of lesser omental deposit, resection of small bowel mesenteric nodules
Histopathology	HPV independent gastric type adenocarcinoma of the uterine cervix Stage IV B

Q. What Are the Unique Clinico Pathological Features of HPV Independent Gastric Type Adenocarcinoma of Cervix?

Gastric-type endocervical adenocarcinoma (ECAC) is a non HPV associated subtype of ECAC, defined by its morphologic similarity to gastric pyloric glands and immunophenotypic expression of gastric-type mucin including MUC6 and HIK1083 [12]. The nuclei are typically basally oriented and show low levels of mitotic activity and apoptosis in contrast to usual-type ECAC. p16 is generally negative or only focally positive, reflecting its HPV-independent pathogenesis. Recent studies have shown that up to 50% of cases show a mutant-type pattern of p53 staining (with either diffusely positive or null staining). PAX8 is positive in 68–88% of cases. In addition, the tumor usually is positive for CK7 and CEA, may be positive for CK20 and CDX2, and is usually negative for ER and PR [3]. Some

cases may be seen in association with lobular endocervical gland hyperplasia (LEGH) and it also has a well-documented association with Peutz-Jeghers syndrome [10].

The mean age of presentation is approximately 50–55 years, around one decade older than patients with usual-type ECAC [13]. The sensitivity of detection in cytology in well differentiated cases is not high [14]. Patients may present with abnormal bleeding, watery vaginal discharge, abdominal discomfort, or may be asymptomatic.

Q. What Is the Oncological Outcome of Gastric Type Cervical Adenocarcinoma

These tumours have an aggressive clinical course and are associated with early peritoneal dissemination with spread to ovaries, abdominal wall, peritoneum, omentum and urinary tract. The same findings were also present in our case. These are associated with poor prognostic factors such as bulky mass, deep stromal invasion, LVSI, parametrial invasion, lymph node metastasis, ovarian metastasis and positive peritoneal cytology [15].

Patients with gastric-type ECAC also show a higher rate of recurrence with lower progression-free and disease-specific survival (DSS), the latter being 42% DSS for gastric-type ECAC compared to 91% for usual-type ECAC which was independent of tumor grade [16]. Patients with gastric-type ECAC display a poorer response rate to chemotherapy and radiotherapy compared to usual-type ECAC [10, 17]. The high rates of chemoresistance and radioresistance in gastric-type ECAC have led investigators to consider alternative molecular-based targeted therapies to potentially achieve better outcomes in these patients. The patient in this case is on follow up for three years and has not recurred. This is not a routine plan for stage IV disease, but considering the rare tumor, treatment can be individualised and discussion in MDT meetings is encouraged. Patient counselling is very crucial in these cases as extensive surgeries don't always translate into survival benefit. Majority of centres adopt the palliative pathway and give systemic therapy.

Key Points

1. Non HPV associated cervical cancer are rare tumours and constitute around 5–10% of all cervical cancers
2. These are associated with unique pathological features especially characterized by absence of p16
3. They are aggressive tumours and are associated with worse oncologic outcomes
4. Although the management strategies are similar to the usual type adenocarcinomas, the response is variable to standard protocols.

References

1. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009;384:260–5.
2. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131:2349–59.
3. WHO Classification of Tumours Editorial Board. Female Genital Tumours. In: WHO classification of tumours: female genital tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2020. p. 631.
4. Fernandes A, Viveros-Carreño D, Hoegl J, Ávila M, Pareja R. Human papillomavirus-independent cervical cancer. Int J Gynecol Cancer. 2022;32(1):1–7.
5. Hart WR. Symposium part II: special types of adenocarcinoma of the uterine cervix. Int J GynecolPathol. 2002;21(4):327–46.
6. Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, et al. International endocervical adenocarcinoma criteria and classification (IECC): a new Pathogenetic classification for invasive adenocarcinomas of the endocervix. Am J Surg Pathol. 2018;42(2):214–26.
7. Dierickx A, Göker M, Braems G, Tummers P, Van den Broecke R. Mesonephric adenocarcinoma of the cervix: case report and literature review. Gynecol Oncol Rep. 2016;17:7–11.
8. Höckel M. Laterally extended endopelvic resection (LEER)--principles and practice. Gynecol Oncol. 2008;111(2 Suppl):S13–7.
9. Ju B, Wang J, Yang B, Sun L, Guo Y, Hao Q, Wu J. Morphologic and immunohistochemical study of clear cell carcinoma of the uterine endometrium and cervix in comparison to ovarian clear cell carcinoma. Int J Gynecol Pathol. 2018;37(4):388–96.

10. Stolnicu S, Karpathiou G, Guerra E, Mateoiu C, Reques A, Garcia A, Bart J, Felix A, Fanni D, Gama J, Hardisson D, Bennett JA, Parra-Herran C, Oliva E, Abu-Rustum N, Soslow RA, Park KJ. Clear cell carcinoma (CCC) of the cervix is a human papillomavirus (HPV)-independent tumor associated with poor outcome: a comprehensive analysis of 58 cases. Am J Surg Pathol. 2022;46(6):765–73. Erratum in: Am J SurgPathol. 2022 Sep 1;46(9): 1317
11. Yang L, Zheng A, Zhang X, Fang X, Sun W, Chen Y. Clear cell carcinoma of the uterine cervix: a clinical and pathological analysis of 47 patients without intrauterine diethylstilbestrol exposure. Int J Gynecol Cancer. 2017;27(5):1009–14.
12. Lin M, Kim KR, Ro J. Gastric-type endocervical adenocarcinoma: review of clinicopathologic characteristics and recent advances. J Gynecol Res Obstet. 2020;6(3):072–5.
13. Pirog EC, Park KJ, Kiyokawa T, Zhang X, Chen W, et al. Gastric-type adenocarcinoma of the cervix: tumor with wide range of histologic appearances. Adv Anat Pathol. 2019;26:1–2.
14. Turashvili G, Morency EG, Kracun M, DeLair DF, Chiang S, et al. Morphologic features of gastric-type cervical adenocarcinoma in small surgical and cytology specimens. Int J Gynecol Pathol. 2019;38:263–75.
15. Nishio S, Mikami Y, Tokunaga H, Yaegashi N, Satoh T, et al. Analysis of gastric-type mucinous carcinoma of the uterine cervix- an aggressive tumor with a poor prognosis: a multi- institutional study. Gynecol Oncol. 2019;153(1):13–9.
16. Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, et al. Gastric type endocervical adenocarcinoma: an aggressive tumor with unusual metastatic patterns and poor prognosis. Am J Surg Pathol. 2015;39:1449–57.
17. Kojima A, Shimada M, Mikami Y, Nagao S, Takeshima N, et al. Chemoresistance of gastric-type mucinous carcinoma of the uterine cervix: a study of the Sankai Gynecology Study Group. Int J Gynecol Cancer. 2018;28:99–106.

Part III

Case Based Studies: Endometrial Cancer

15 Diagnostic Pathways of Postmenopausal Bleeding

Alexandra Bouzouki and Ayman Ewies

Introduction

Postmenopausal bleeding (PMB) is defined as any vaginal bleeding that occurs 12 months after spontaneous cessation of menstruation in women >40 years of age who are not pregnant or lactating. It also includes unscheduled bleeding 6 months after starting hormone replacement therapy (HRT) as well as postcoital bleeding [1].

The majority of women with endometrial hyperplasia or cancer present with PMB as the only complaint [2]. Currently, more than 1900 British women die from endometrial cancer every year in the UK; therefore, NICE guidelines recommend referral using a suspected cancer pathway for an appointment within 2 weeks for clinical evaluation to rule out malignancy [3]. PMB is a common condition affecting 7–15% of postmenopausal women, and the prevalence of endometrial cancer ranged in various studies from 3% to 10%. PMB accounts for >5% of all gynaecological consultations [1, 4, 5].

A. Bouzouki
Department of Gynaecology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
e-mail: alexandra.bouzouki1@nhs.net

A. Ewies (✉)
Department of Gynaecology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Aston Medical School, University of Aston, Birmingham, UK
e-mail: ayman.ewies@nhs.net; ewiesa@aston.ac.uk

It is well-established that management strategies using trans-vaginal ultrasound scanning (TVS), as an initial tool of investigation are safe, cost-effective, and has minimised the need for more invasive endometrial evaluation with endometrial sampling and hysteroscopy. TVS measurement of endometrial thickness (ET) of ≤4 mm is associated with low risk (<1%) of endometrial cancer and it would be justified to refrain from further investigations in these cases. However, if the ET is >4 mm then endometrial biopsy is recommended [2]. Hysteroscopy is offered to women with ET of ≥10 mm, focal lesion on TVS, recurrent PMB irrespective of the ET, or inadequate endometrial biopsy. Tamoxifen users with PMB are routinely also offered hysteroscopy [1, 4–6].

Nonetheless; there are many controversial grey areas as regards the management of PMB. There is lack of consensus as regards the definition of recurrent PMB i.e., the time interval to reinvestigate women with previous negative investigations, and whether these women have a higher risk of endometrial cancer. It is not also clear whether benign-looking small endometrial polyps with normal background endometrium ought to be removed. Other unanswered questions relate to the management of the incidental finding of ET >4 mm in the absence of PMB, the

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_15

long-term management of obese women diagnosed with hyperplasia without atypia who responded to short term progestogen therapy, and the clinical value of finding fluid in the cavity on TVS.

In this chapter, we are presenting a few clinical scenarios, from every day practice, to touch on some of the controversial areas of management taking into consideration the current best available evidence.

Case 1: Post Menopausal Bleeding in Tamoxifen Users

Age, Parity, PS	54-year-old Mrs. K, para3, PS-0
Clinical presentation	Intermittent mild vaginal bleeding for 6 weeks. Last normal period at age of 49 History of left breast lumpectomy for cancer (ER +ve, PR +ve, HER2 negative) 3 years ago and is taking tamoxifen 20 mg once daily **Clinical examination**: BMI of 40, normal vital signs, and unremarkable gynaecological examination
Co morbidities	Obesity
Transvaginal sonography	Normal uterus and ovaries apart from thickened endometrium of 13 mm with cystic spaces
Hysteroscopy	Showed thickened polypoidal endometrium with areas of calcification. There were no well-formed polyps as such
Endometrial biopsy	Endometrial hyperplasia without atypia

Q. What Is the Impact of Tamoxifen on the Endometrium and What Is Its Influence in the Diagnosis of PMB?

Tamoxifen, selective oestrogen receptor modulator (SERM), has an anti-estrogenic effect on breast cells (antagonist) but a light oestrogenic effect on uterus and vagina (agonist). Therefore, women presenting with PMB on Tamoxifen are at increased risk of developing endometrial hyperplasia and/or cancer and should be made aware to report any vaginal bleeding [2].

Q. What Are the Ultrasound Features of Tamoxifen Induced Hyperplasia? Should These Women Be Periodically Screened?

Ultrasound features of Tamoxifen induced hyperplasia include thickened endometrium frequently with cystic changes and endometrial polyp formation [7]. A prospective case-control study was carried out to assess the value of elastosonography in identifying endometrial pathology in 66 Tamoxifen users *v/s* 122 healthy controls. A significant positive correlation was found between duration of tamoxifen usage and ET, which was a predictor for the risk of endometrial hyperplasia and cancer. The study proposed an ET threshold of 7.8 mm (92% sensitivity, 43% specificity) with a threshold duration of use of 32 months (58% sensitivity, 100% specificity) to predict the risk in postmenopausal women [8].

There is no clear guidance to inform clinical practice as whether periodic screening of asymptomatic women on Tamoxifen is safe or cost-effective and whether the most appropriate tool would be TVS or endometrial biopsy. Regular screening is predicted to lead to overtreatment, increased patient anxiety and potentially compromise patient compliance with the medication [9]. The British Gynaecological Cancer Society (BGCS) guidelines recommend that routine screening with TVS, endometrial biopsy, or both has not been shown to be effective in patients on tamoxifen. (Grade C). Postmenopausal women taking tamoxifen should be routinely questioned at breast cancer follow-up visits about symptoms of vaginal bleeding/discharge and should be made aware of the risks [10]. The current practice, therefore, is to refer these women through the suspected cancer pathway for an appointment within 2 weeks only if they develop PMB [9, 11].

Q. What Is the Diagnostic Work-Up for Tamoxifen Users Who Develop PMB?

The investigation work-up for these women should include hysteroscopy [12]. The British

Gynaecological Cancer Society (BGCS) guidelines recommend that PMB in Tamoxifen users should be investigated with hysteroscopy as well as TVS and endometrial biopsy (Grade D) [10].

Q. What Is the Management of Tamoxifen-Induced Endometrial Hyperplasia Without Atypia?

Women who develop endometrial hyperplasia whilst on Tamoxifen require a multidisciplinary team (MDT) approach by breast oncologists and gynaecological oncologists to make the management plan.

Generally speaking, hyperplasia should be treated based on histological classification (i.e., with or without atypia). The standard treatment of endometrial hyperplasia without atypia in postmenopausal women is progestogen therapy. The Royal College of Obstetricians and Gynaecologists Green-Top guideline states that the levonorgestrel-releasing intra-uterine system (LNG-IUS) should be the first-line medical treatment because, compared with oral progestogens, it has a higher disease regression rate with a more favourable bleeding profile and fewer adverse effects [2].

The dilemma is that the WHO Medical Eligibility Criteria for Contraceptive Use stated that the use of LNG-IUS is classified as category 4 in women with current breast cancer and as category 3 in women with a past history of breast cancer with no evidence of disease for 5 years. Category 3 means "a condition where the theoretical or proven risks usually outweigh the advantages of using the method" and category 4 means "a condition which represents an unacceptable health risk if the method is used". The same criteria are adopted by Faculty of Sexual and Reproductive Health, UK and Centers for Disease Control and Prevention, US [13–16].

Therefore, the management of hyperplasia without atypia in Tamoxifen users should be individualised by the MDT taking into account the body mass index (BMI) and other risk factors. The options of expectant management with 6 monthly endometrial biopsy and hysterectomy should be discussed with women.

Q. Does LNG-IUS have a Role in Endometrial Protection in Tamoxifen Users in the Current Practice?

The endometrial protective effect of LNG-IUS is debatable. A small observational study by Philip et al., including 20 postmenopausal breast cancer survivors treated with Tamoxifen, found increased expression of a decidualisation marker IGFBP-1 (Insulin like growth factor binding Protein-1) in endometrial biopsies obtained 12 months after insertion of LNG-IUS suggesting a protective action against endometrial cancer. The authors argued that there is no evidence that its use is detrimental to the risk of recurrence of breast cancer [17]. A Cochrane review assessing the use of LNG-IUS for endometrial protection in women with breast cancer on tamoxifen, including four trials and 543 women, reported no clear evidence that the LNG-IUS affects the risk of breast cancer recurrence. However, the quality of evidence was judged as moderate due to small sample sizes and low event rates for the outcome comparisons. Interestingly, there was no evidence that using LNG-IUS reduces the risk of endometrial cancer in tamoxifen users [18]. Therefore; the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines stated that even though there is some evidence that LNG-IUS may prevent hyperplasia in women on Tamoxifen, the effect on breast cancer recurrence remains uncertain; therefore, its routine use for protection is not recommended [2].

Case 2: Hyperplasia with Atypia in Women with High BMI

Age, Parity, PS	58-year-old Mrs. S, Nulliparous, PS-2
Clinical presentation	One episode of vaginal bleeding similar to a period. Last normal period was 4 years ago. **Clinical examination**: BMI 49, normal vital signs, and inconclusive gynaecological examination

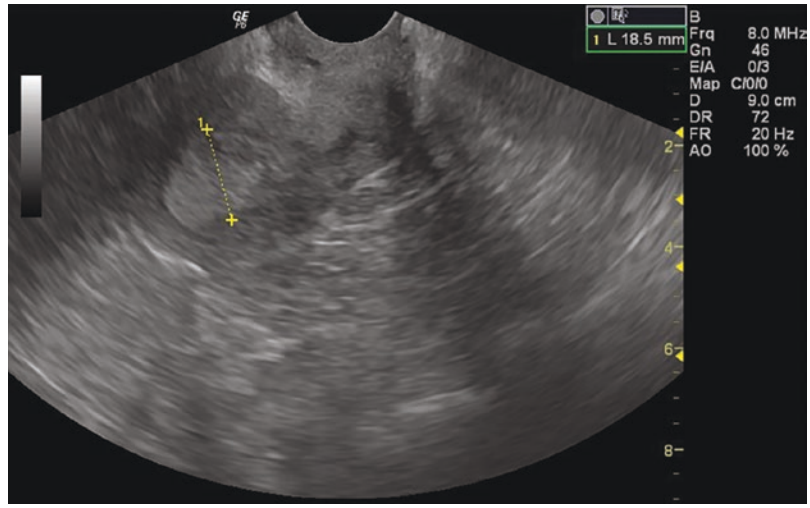


Fig. 15.1 TVS showing ET = 18 mm in women with post menopausal bleeding diagnosed as atypical hyperplasia

Co morbidities	Hypertension, Type 2 diabetes mellitus, hypercholesterolemia, two coronary stents inserted, obstructive sleep apnoea and knee arthritis. On multiple medications for these conditions including anti-coagulation and continuous positive airway pressure (CPAP)
Transvaginal sonography	Normal uterus and ovaries apart from thickened endometrium of 18 mm. (Fig. 15.1)
Hysteroscopy	Thickened irregular endometrium with no necrotic or haemorrhagic tissues
Endometrial biopsy	Endometrial hyperplasia with atypia

Q. What Is the Relation Between Obesity and Endometrial Hyperplasia and Cancer?

Endometrial hyperplasia is caused by the proliferative effect of excess oestrogen on the endometrium when unopposed by progesterone. In high BMI women, there is excessive peripheral conversion of androgen to oestrogen in the adipose tissue increasing the circulating oestrogen, which in the absence of natural progesterone in post-menopausal women exposes them to a higher risk of endometrial hyperplasia and/or cancer [19]. At least 41% of endometrial cancers were attributed to obesity (BMI >30 kg/m^2), with each 5 kg/m^{2}increase in BMI being linearly associated with a higher risk. On the other hand, sustained weight loss reduces this risk [20].

Q. What Are the Challenges in Management of High Surgical Risks Patients with Endometrial Hyperplasia?

In women with hyperplasia without atypia, the risk of progression to cancer is <5% over 20 years; progestogen therapy or expectant management may suffice [2]. In hyperplasia with atypia, the risk of progression is 8% over 4 years and the risk of co-existing endometrial cancer is 43%; therefore, more definite treatment is required which is a total hysterectomy and bilateral salpingo-oophorectomy [2]. Nonetheless, the management of endometrial hyperplasia with atypia in obese women with multiple surgical and anaesthetics risk factors is challenging. The treatment strategies addressing the reversible risk factors (e.g., obesity and HRT usage) and progestogenic therapy (oral or LNG-IUS) with regular endometrial biopsies for follow up may be considered by the gynaecological oncology MDT. A retrospective study, including 245 women with hyperplasia with atypia and mean

BMI of 40, suggested that treatment with LNG-IUS is more effective than oral progestogen therapy with a complete response of 78.7% *v* 46.7% (95% CI 2.39–4.62) respectively. Moreover, the risk of progression to cancer was lower in the LNG-IUS group (4.5% vs 15.7%; 95% CI, 0.11–0.73) [21]. This may be attributed to the higher endometrial tissue concentrations of progestogen in LNG-IUS users as well as the impact of obesity on oral steroid hormone absorption, volume of distribution and metabolism [22]. Patient compliance also plays a role in the apparent superiority of the LNG-IUS over oral progestogen therapy [23]. The Royal College of Obstetricians and Gynaecologists guidelines stated that the LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease regression rate with a more favourable bleeding profile and fewer adverse effects [2].

Q. Are There Any Biomarkers Associated with Response to Progestogen Therapy in Women with Endometrial Hyperplasia or Cancer?

Multiple markers have been investigated including (1) Gene-based biomarker such as PTEN, p53, MicroRNAs in body fluids, DNA methylation biomarker, circulating tumour DNA (ctDNA), DNA polymerase epsilon (POLE) and MMR-D, (2) Protein biomarkers such as pRb2/p130, angiogenesis factors, Ki-67, Cell adhesion molecules (CAMs), ARID1A, pHH3, (3) Blood-based biomarkers such as Human Epididymis protein 4 (HE4) used either alone or alongside markers such as CA-125, CA724 and CA19-9, serum amyloid-A (SA-A) and YKL-40 & DKK-3, (4) Hormonal biomarkers such as oestrogen receptor, progesterone receptor and HER2, and (5) Tissue-based biomarkers such as tumour-infiltrating lymphocytes (TILs) and tumour-associated macrophage (TAM) [24].

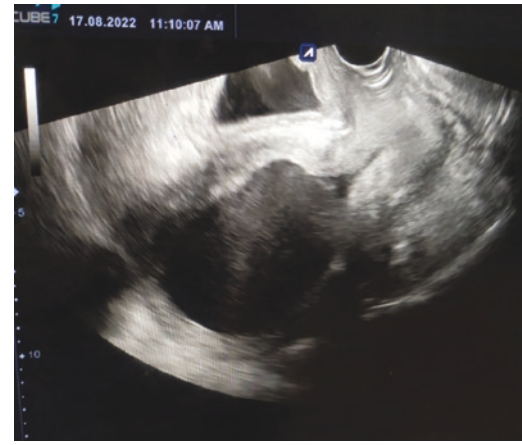


Fig. 15.2 TVS scan showing pyometra

However, none of these biomarkers was proven to be ideal in terms of reducing the need for invasive diagnostic tests, being reproducible to enable identify "low-risk" tumours and guide treatment and prognosis, and/or cost-effectiveness. Therefore; currently there is no routinely used biomarkers in endometrial cancer for diagnostic or prognostic purposes and further research is required to validate them in guiding clinical practice [24, 25].

Case 3: Fluid in the Uterine Cavity

Age, Parity, PS	87-year-old Mrs. Y, para 5, PS-1
Clinical presentation	Pinkish discharge in the tissues on wiping herself happening on a few occasions BMI of 23, normal vital signs, and vaginal atrophy on gynaecological examination
Co morbidities	Arthritis
Transvaginal sonography	Small atrophic uterus and both ovaries could not be visualized. Collection in uterine cavity s/o pyometra 5 × 4 × 3.5 cm (Fig. 15.2)
Hysteroscopy	No tissues were obtained on blind endometrial sampling in the outpatient; hence hysteroscopy was performed. It showed atrophic endometrium
Endometrial biopsy	Inadequate for opinion

Q. How Is ET Measured When There Is Fluid in the Uterine Cavity?

The endometrial thickness is measured on either side of the intra-cavitary fluid in the sagittal plan, and the fluid should not be included in the measurement [7, 26].

Q. What Are the Causes of Fluid Presence in the Uterine Cavity?

There are essentially three types of fluid: hydrometra which is simple fluid**,** haematometra with haemorrhagic content or clots and pyometra with pus [7, 26]. Whereas in premenopausal women, endometrial fluid can be caused by a benign condition such as cervical stenosis, imperforate hymen or even physiological, in postmenopausal women it can often be a concern. Possible reasons include cervical stenosis, endometrial polyp, use of HRT or malignancy [7].

Q. What Is the Risk of Malignancy When There Is Fluid in the Uterine Cavity?

A prospective study, including 128 women with PMB, assessed the association of fluid in the uterine cavity on TVS with endometrial pathology. It was concluded that the presence of fluid is a good marker of malignancy only if the ET is >4 mm in women with PMB. These women are offered endometrial biopsy anyway. If the ET is ≤4 mm, the presence of intra-cavitary fluid is not an indication for further invasive investigation; however, adnexal and cervical pathology should be excluded by TVS and speculum examination, respectively. The least ET was 12 mm in women with cancer, 7 mm in those with hyperplasia and 5 in those with benign polyps [26]. Endometrial biopsy and/or hysteroscopy is indicated if the endometrium is not well demonstrated and the cavity is over distended with fluid as in cases of pyometra or hematometra [11, 26].

Case 4: Recurrent PMB

Age, Parity, PS	72-year-old lady Mrs. A, para 2, PS-1
Clinical presentation	Experienced two episodes of mild vaginal bleeding She presented with PMB 15 months ago when the TVS revealed ET of 3 mm and she was reassured and discharged **Clinical examination**: BMI 26, normal vital signs, and unremarkable gynaecological examination
Co morbidities	Hypertension and asthma
Transvaginal sonography	Normal uterus and ovaries with irregular endometrium of 9 mm.
Hysteroscopy	Atrophic endometrium with 2 cm polyp near the left ostia. The polyp was morcellated in the outpatient
Endometrial biopsy	Benign polyp

Q. What Is the Definition of Recurrent PMB?

Recurrent PMB is defined as bleeding episodes that recurred, after negative investigations at first referral, necessitating a new referral to the PMB clinic by the family doctor. The recurrence interval is defined as the period between the date of referral for the first episode to the date of referral for the subsequent episode as per the family doctor's referral letter [1].

The prevalence of recurrent PMB varied in published reports between 4 and 33% [27], which may reflect the variations in the definition. There is no universal definition in the literature, and some studies mixed women who were re-referred with recurrent PMB after negative initial investigations with women who suffered multiple episodes of bleeding before they were referred for the first time. Ghoubara et al. documented that women who are re-referred with recurrent PMB either have pathology missed during initial investigations or have risk factors to develop endometrial pathology. This should not be confused with late presentation or late referral, which highlights

issues around access to care rather than underlying risk of pathology [1].

Q. What Is the Common Causes of Recurrent PMB?

An observational prospective study of 1902 women with PMB; of them 385 presented with recurrent PMB, found a higher rate of endometrial polyps (20.8% *v* 14.1%, $p = 0.002$) and a lower rate of endometrial hyperplasia and/or cancer (8.3% v 10.5%, $p = 0.21$) in those with recurrent PMB when compared with women presented with single episode. On comparing to women with a single referral, the odds ratio (95% CI) for women with multiple referrals because of recurrent PMB to have endometrial polyps was 1.6 (1.2–2.1) [1].

Similarly, a prospective study, comparing women with multiple referrals with recurrent PMB ($n = 106$) *v/s* those with a single referral episode ($n = 1832$), found that the prevalence of endometrial hyperplasia or cancer was significantly less (6.6% v. 14.4%, $p = 0.04$) and the prevalence of benign endometrial polyps was significantly higher (28% v 19%, $p = 0.02$) in women with recurrent PMB [28]. Another retrospective study, comparing women with multiple referrals with recurrent PMB ($n = 126$) *v/s* those with a single referral episode ($n = 1430$), reported no difference in the prevalence of endometrial cancer between the two groups over a 56-month period [27].

Q. What Is the Diagnostic Pathway in Women with Recurrent PMB?

In contrast to the standardised approach to investigating initial episodes of PMB, management of recurrent PMB is ambiguous. There is a great deal of diversity amongst gynaecologists despite it being a common clinical problem. Little is known about the interval for re-investigation, i.e., the time after which women should be re-investigated if they are re-referred with recurrent PMB after negative initial investigations, with some investigators recommending a 6-month interval [27]. Ghoubara et al. found the median recurrence interval to be 24 months (IQR 13–47 months) with no case of endometrial hyperplasia or cancer was diagnosed in the first 10 months after negative initial investigations [1]. The European Menopause and Andropause Society (EMAS) clinical guidelines suggested that women with recurrent or persistent bleeding should be followed up after 6 months. A combination of TVS, hysteroscopy to directly visualize the uterine cavity, and biopsy was advised. However, this guideline has not been updated since 2013 [29].

Although the first line management of PMB includes TVS ± endometrial biopsy at initial presentation, women with recurrent PMB warrant a hysteroscopy irrespective of endometrial thickness to exclude endometrial polyps [1]. Although the vast majority of endometrial polyps are benign and the consequences of diagnosis are deemed less serious than endometrial hyperplasia or cancer, they are frequently associated with abnormal uterine bleeding. Removal frequently resolves symptoms, preventing further referrals and alleviating women's anxiety [30]. The guidelines of the Canadian Society of Obstetricians and Gynaecologists state that hysteroscopic examination should be considered in women with persistent or recurrent uterine bleeding with negative initial investigations, irrespective of the menopausal status (II-2B) [31].

Some investigators suggested that the increase in prevalence of endometrial polyps in women with recurrent PMB may reflect the higher accuracy of hysteroscopy for detecting focal disease when used at the second presentation, i.e., polyps are missed at first presentation when TVS is used as the first-line investigation [32]. Nevertheless, Ghoubara et al. suggested that polyps de novo may develop more frequently, accounting for further bleeding symptoms because the prevalence of polyps in their series was highest in the 108 women with recurrent PMB who had polyps resected at first presentation. Of them, 50 (46.3%) were found to have polyps in the subsequent presentations, with a median recurrence interval of 27 months (IQR 15–52 months) [1].

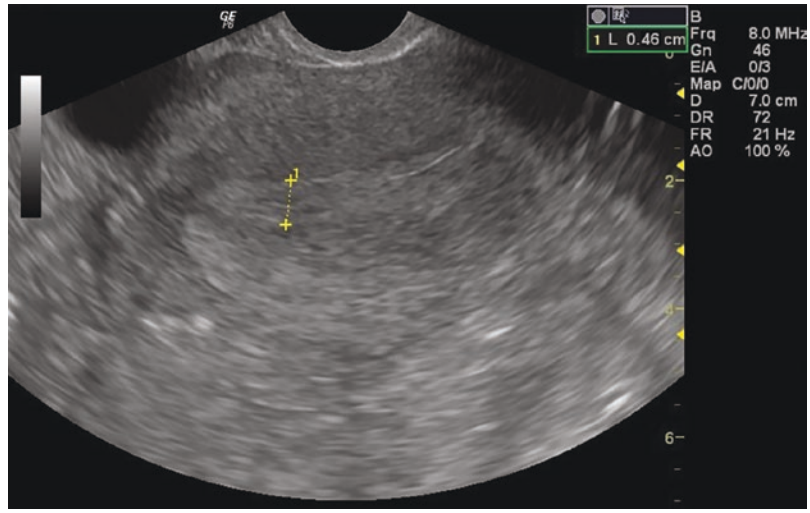


Fig. 15.3 TVS showing regular smooth endometrium and ET of 7.5 mm in asymptomatic post menopausal woman

Case 5: Incidental Finding of Thickened Endometrium

Age, Parity, PS	65-year-old, Mrs. B, para 1, PS-0
Clinical presentation	Referred to the PMB clinic by the family doctor because of an incidental finding of 7.5 mm endometrium on TVS performed to investigate abdominal pain. She has never experienced PMB since menopause at age of 53 BMI 31, normal vital signs, and unremarkable gynaecological examination
Co morbidities	Irritable bowel syndrome and reflux oesophagitis
Transvaginal sonography	Normal uterus and ovaries with regular smooth endometrium and ET of 7.5 mm. (Fig. 15.3)

Q. What Is the Clinical Significance of the Incidental Finding of Thickened Endometrium in Postmenopausal Women with no PMB?

There is no evidence-based guidelines to inform clinical practice as regards the significance of the incidental finding of ET >4 mm on TVS in postmenopausal women without PMB or how these women are best managed, leading to wide variations in practice.

It is well established that ET ≤4 mm in women with PMB is associated <1% risk of endometrial cancer; therefore, these women are usually reassured without the need for further investigations [2]. However, in postmenopausal women without PMB, the threshold that separates normal from pathologically thickened endometrium has not been standardised.

More than 90% of women with endometrial cancer present with PMB, and women with PMB have a 5–10% chance of having endometrial cancer [33]. However, it is estimated that up to 15% of endometrial cancers occur in women without PMB [34]. In addition, two studies found that endometrial polyps are the commonest pathology encountered in postmenopausal women with an asymptomatic increase in ET. The reported prevalence varied between 34% and 73%, and a hysteroscopy was recommended as the first-line investigation tool [4, 35].

Q. What Is the Endometrial Thickness Cut-Off that Triggers Investigations in Postmenopausal Women with no PMB?

Smith-Bindman et al. performed a decision analysis study, in a theoretical cohort of 10,000 postmenopausal women aged ≥50 years using published and unpublished data, to determine the ET threshold that should be considered abnormal

in asymptomatic postmenopausal women. They found that in a postmenopausal woman with PMB, the risk of endometrial cancer is approximately 0.07% if the endometrium is thin (≤5 mm) and 7.3% if her endometrium is thick (>5 mm). In a postmenopausal woman without PMB, an 11 mm threshold yields a similar separation between women who are at high risk and low risk for endometrial cancer. The risk of cancer is approximately 0.002% if the endometrium is thin (≤11 mm) and 6.7% if the endometrium is thick (>11 mm). If an ET threshold of 4 mm was used to define an abnormal test result, as in women with PMB, the number of false-positive test results would far outnumber the true-positive test results [28].

In a study, including 1995 women attending PMB clinic; of them 81 (4.1%) were referred because of ET >4 mm without PMB, found that the prevalence of atypical endometrial hyperplasia and cancer was 4/81 (4.9%) and endometrial polyps was 20/81 (24.7%). On using a receiver operator characteristic curve, the diagnosis of endometrial atypical hyperplasia and cancer using the ET threshold of ≥10 mm had a sensitivity of 100% (95% CI = 40–100%), a specificity of 60% (95% CI = 48–71%) with AUC = 0.8 (95% CI = 0.66–0.93), $p = 0.04$. For the 35 women with an ET ≥ 10 mm, the prevalence of endometrial atypical hyperplasia and cancer was 4/35 (11.4%) and benign endometrial polyps was 16/35 (45.7%). The use of ≥10 mm ET threshold to prompt investigations did not miss any case of endometrial atypical hyperplasia or cancer in this series [4]. Similarly, Giannella et al. tested the diagnostic accuracy of various ET cut-off values by comparing histological and hysteroscopic findings in asymptomatic postmenopausal women with ET > 4 mm. They found that an ET cut-off value of >10 mm did not miss any cases of endometrial atypical hyperplasia or cancer. At this cut-off value, the atypical hyperplasia and cancer rate was 9.4%. On using ET cut-off value >4 mm, 97% of performed hysteroscopies revealed a benign intra-uterine pathology [36].

Case 6: Endometrial Polyps

Age, Parity, PS	62-year-old Mrs. S, para 2, PS-0
Clinical presentation	Experienced 2 episodes of PMB. Last natural period was at age of 55. BMI 28, normal vital signs, and unremarkable gynaecological examination
Co morbidities	Nil
Transvaginal sonography	Irregular endometrium with ET of 15 mm with normal vascularity
Hysteroscopy	Endometrial polyp of 2.5 cm approximately. Background endometrium was normal. The polyp was morcellated.
Histology	Inactive endometrium, benign polyp

Q. What Is the Prevalence of Endometrial Hyperplasia or Cancer in Polyps Diagnosed in Women with PMB?

The exact prevalence of endometrial polyps in postmenopausal women is unknown because many polyps are asymptomatic. A recent meta-analysis showed that the pooled estimate of prevalence of hyperplasia and cancer in women with PMB was 9% (95% CI = 6.5%–11.5%) [5, 37]. The National Institute for Health and Care Excellence (NICE) sets a 3% positive predictive value cut-off to trigger referrals to secondary care for investigations for suspected cancer [3]. The lower limit of the 95% CI in the meta-analysis sets comfortably above this 3% threshold suggesting that endometrial polyps in women with PMB warrant removal for histopathological assessment even if the background endometrium is normal [5, 37].

Q. What Are the Hysteroscopic Features Suggestive of Hyperplasia or Cancer in Endometrial Polyps?

One of the problems that investigators encountered when reporting on endometrial polyps is the

lack of robust hysteroscopic features that could be associated with higher risk of hyperplasia and cancer in polyps. Therefore, until such criteria are established, the option of expectant management should only be considered with caution. These criteria could be related to the polyp size, surface irregularity and vascularity. A small retrospective study, including a mixture of symptomatic (n = 20) and asymptomatic (n = 40) postmenopausal women, reported that the hysteroscopic appearance did not provide a safe method of differentiating polyps with hyperplasia and cancer from benign ones. Although all polyps appeared benign on hysteroscopic examination, histological assessment showed three cases of cancer and atypical hyperplasia. These three cases were asymptomatic and had normal endometrium [5].

Q. What Are the Predictors of Endometrial Hyperplasia or Cancer in Postmenopausal Women with Endometrial Polyps?

A large series of 421 women, with hysteroscopically benign-looking endometrial polyps with normal background endometrium attending PMB clinic, found the prevalence of endometrial hyperplasia and cancer to be 8%. The risk of hyperplasia and cancer in polyps was 5.5-fold and 3.5-fold higher in women with endometrial thickness ≥10.8 mm (reflecting the size of polyp) and in women with body mass index ≥32.5 kg/m^2, respectively. Women with bothET≥10.8 mm and BMI ≥32.5 kg/m^2 had a sevenfold higher risk. Age, years since last period, ethnicity, recurrent PMB, diabetes, hypertension, and the use of tamoxifen did not differ between the outcome groups [5].

Q. Should All Endometrial Polyps Be Removed in Postmenopausal Women?

There is lack of consensus amongst gynaecologists as regards removal of endometrial polyps at first presentation. The advocates for routine polypectomy argue that polyps may be associated with recurrent PMB in addition to the risk of hyperplasia or cancer [5, 38]. The opponents believe that see-and-treat management is only based on experts' opinions and few published data, and polypectomy may be subjecting women to unnecessary interventions and wasting valuable health-care resources [39]. An RCT was designed to evaluate the efficacy of endometrial polyp removal where women with PMB were asked whether they could be allocated for immediate removal or expectant management. The trial was discontinued after 26 months because of lack of recruitment to the expectant management arm. Most women and doctors deemed office hysteroscopy to be a rather minimal invasive procedure and opted for allocation to the hysteroscopic polypectomy arm [39].

The previously mentioned meta-analysis provides the best current evidence with the findings suggesting that women with PMB should be offered removal of endometrial polyps [5, 37]. The Guidelines of the American Association of Gynaecologic Laparoscopists recommend that expectant management is reasonable, for small polyps and in asymptomatic women (Level A) [40]. However, removal for histological assessment is appropriate in women with PMB (Level B) [40]. There is grade II evidence that small polyps may spontaneously regress in approximately 25% of cases, with smaller polyps (≤10 mm) are more likely to regress [38].

Key Points

1. No evidence of routine screening of women on Tamoxifen but investigations should be triggered if they develop PMB. The investigation work-up for these women should include hysteroscopy rather than relying on TVS and/or endometrial biopsy alone.
2. Given the uncertainty of safety of progestogen therapy, the management of hyperplasia without atypia in tamoxifen users should be individualised and options of expectant management with 6 monthly endometrial biopsy or hysterectomy may be offered. Routine use of LNG-IUS for endometrial protection is not recommended.
3. The standard treatment of hyperplasia with atypia is total hysterectomy with bilateral salpingo-oophorectomy. Progestogen therapy (preferably) LNG-IUS may be offered in

selected cases upon the decision of gynaecological oncology MDT when women are deemed to be at high risk for surgery or would like to preserve fertility.

4. Currently, there is no routinely used biomarkers in endometrial cancer for diagnostic or prognostic purposes and further research is required to validate them in guiding clinical practice.
5. The presence of fluid in the uterine cavity may be a marker of malignancy only if the ET is >4 mm in women with PMB. Endometrial biopsy and/or hysteroscopy is indicated if the endometrium is not well demonstrated and the cavity is over distended with fluid as in cases of pyometra or hematometra.
6. Women with recurrent PMB have higher risk of endometrial polyps rather than endometrial hyperplasia or cancer when compared with those with single episode of referral. Hysteroscopy should be included in the work-up of women with recurrent PMB to rule out endometrial pathology primarily polyps.
7. The use of 10 mm ET threshold to prompt investigations in asymptomatic postmenopausal women may be acceptable since there was no missed cases of atypical endometrial hyperplasia or cancer in observational studies.
8. The prevalence of hyperplasia and cancer in benign-looking polyps is high (9%). The independent predictors of hyperplasia and cancer in endometrial polyps are increased body mass index and endometrial thickness and removal of endometrial polyps is warranted in women with PMB since there is no hysteroscopic morphological criteria that can reliably predict the outcome.

References

1. Ghoubara A, Sundar S, Ewies A. Endometrial pathology in recurrent postmenopausal bleeding: observational study of 385 women. Climacteric. 2018;21(4):391–6.
2. Royal College of Obstetricians and Gynaecologists (RCOG). Management of endometrial hyperplasia green-top guideline no. 67; 2016. RCOG/BSGE Joint Guideline. Available from: https://www.rcog.org.uk.
3. National Institute for Health and Clinical Excellence (NICE). Suspected cancer: recognition and referral. NICE guideline NG12; 2015. Last updated 2021. Available from: https://www.nice.org.uk/guidance/ng12.
4. Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women–determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol. 2018;38(8):1146–9.
5. Ghoubara A, Sundar S, Ewies A. Predictors of malignancy in endometrial polyps: study of 421 women with postmenopausal bleeding. Climacteric. 2018;21(1):82–7.
6. Burbos N, Musonda P, Giarenis I, Shiner A, Giamougiannis P, Morris E, et al. Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEFAB risk assessment tool. Br J Cancer. 2010;102(8):1201–6.
7. Takacs P, De Santis T, Nicholas MC, Verma U, Strassberg R, Duthely L. Echogenic endometrial fluid collection in postmenopausal women is a significant risk factor for disease. J Ultrasound Med. 2005;24(11):1477–81.
8. Gultekin I, Imamoglu G, Gultekin S, Yilmaz E, Yilmaz Z, Alkan A, et al. Elastosonographic evaluation of endometrium in women using tamoxifen for breast cancer. Niger J Clin Pract. 2019;22(1):92–100.
9. Neven P, Froyman W, Timmerman S, Timmerman D. Uterine ultrasound and endometrial biopsy in tamoxifen users. Breast Cancer Res Treat. 2020;180(3):833–4.
10. Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C, et al. BGCS uterine cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2017;213:71–97.
11. Bakour SH, Timmermans A, Mol BW, Khan KS. Management of women with postmenopausal bleeding: evidence-based review. Obstetric Gynaecol. 2012;14(4):243–9.
12. Alfhaily F, Ewies AA. The first-line investigation of postmenopausal bleeding: transvaginal ultrasound scanning and endometrial biopsy may be enough. International Journal of GynecologicCancer. 2009;19(5):892–5.
13. Omar OA, Ewies A. Re: the levonorgestrel-releasing intrauterine device induces endometrial decidualisation in women on tamoxifen. J Obstet Gynaecol. 2021;41(2):332.
14. World Health Organization (WHO). Medical eligibility criteria for contraceptive use. Department of Reproductive Health and Research, World Health Organisation. Available from: https://www.who.int/publications/i/item/9789241549158.
15. The Faculty of Sexual and Reproductive Healthcare (FSRH). FSRH UK Medical eligibility criteria for contraceptive use (UK MEC). 2015. Available from: https://www.fsrh.org/ukmec/.
16. Centers for Disease Control and Prevention (CDC); Contraceptive Guidance for Health Care Providers; US Medical Eligibility Criteria (US MEC) for contra-

ceptive use. 2016. Available from: https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html.
17. Philip S, Taylor AH, Konje JC, Habiba M. The levonorgestrel-releasing intrauterine device induces endometrial decidualisation in women on tamoxifen. J Obstet Gynaecol. 2019;39(8):1117–22.
18. Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev. 2015;(12):CD007245.
19. Schmandt RE, Iglesias DA, Co NN, Lu KH. Understanding obesity and endometrial cancer risk: opportunities for prevention. Am J Obstet Gynecol. 2011;205(6):518–25.
20. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5· 24 million UK adults. Lancet. 2014;384(9945):755–65.
21. Mandelbaum RS, Ciccone MA, Nusbaum DJ, Khoshchehreh M, Purswani H, Morocco EB, et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. Am J Obstet Gynecol. 2020;223(1):103.e1–103.e13.
22. Nilsson C, Haukkamaa M, Vierola H, Luukkainen T, Arcangeli P. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. Clin Endocrinol. 1982;17(6):529–36.
23. Gupta JK, Daniels JP, Middleton LJ, Pattison HM, Prileszky G, Roberts TE, et al. A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. Health Technol Assess. 2015;19(88):1–118.
24. Hutt S, Tailor A, Ellis P, Michael A, Butler-Manuel S, Chatterjee J. The role of biomarkers in endometrial cancer and hyperplasia: a literature review. Acta Oncol. 2019;58(3):342–52.
25. Baxter E, Brennan DJ, McAlpine JN, Mueller JJ, Amant F, Van Gent MD, et al. Improving response to progestin treatment of low-grade endometrial cancer. Int J Gynecol Cancer. 2020;30(11):1811–23.
26. Ćurčić A, Đurđević S, Mihaldžić-Tubić S, Mladenović-Segedi L, Maksimović M. Ultrasound detection of endometrial fluid in postmenopausal women. Med Pregl. 2009;62(7–8):337–41.
27. Ronghe R, Gaudoin M. Women with recurrent postmenopausal bleeding should be re-investigated but are not more likely to have endometrial cancer. Menopause Int. 2010;16(1):9–11.
28. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: a prospective cohort study. J Minim Invasive Gynecol. 2014;21(5):799–803.
29. Dreisler E, Poulsen LG, Antonsen SL, Ceausu I, Depypere H, Erel CT, et al. EMAS clinical guide: assessment of the endometrium in peri and postmenopausal women. Maturitas. 2013;75(2):181–90.
30. Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: a systematic review. J Minim Invasive Gynecol. 2006;13(4):260–8.
31. Renaud M-C, Le T. No. 291-epidemiology and investigations for suspected endometrial cancer. J Obstet Gynaecol Can. 2018;40(9):e703–e11.
32. Van Dongen H, De Kroon CD, Jacobi CE, Trimbos J, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG Int J Obstet Gynaecol. 2007;114(6):664–75.
33. Bachmann LM, Riet G, Clark TJ, Gupta JK, Khan KS. Probability analysis for diagnosis of endometrial hyperplasia and cancer in postmenopausal bleeding: an approach for a rational diagnostic workup. Acta Obstet Gynecol Scand. 2003;82(6):564–9.
34. National Institutes of Health (NIH) National Cancer Institute (NCI). Surveillance, epidemiology, and end results program (SEER). 2000. Available from: https://seer.cancer.gov/.
35. Schmidt T, Breidenbach M, Nawroth F, Mallmann P, Beyer IM, Fleisch MC, et al. Hysteroscopy for asymptomatic postmenopausal women with sonographically thickened endometrium. Maturitas. 2009;62(2):176–8.
36. Giannella L, Mfuta K, Setti T, Boselli F, Bergamini E, Cerami L. Diagnostic accuracy of endometrial thickness for the detection of intra-uterine pathologies and appropriateness of performed hysteroscopies among asymptomatic postmenopausal women. Eur J Obstet Gynecol Reprod Biol. 2014;177:29–33.
37. Ghoubara A, Price MJ, Fahmy MSE-D, Ait-Allah AS, Ewies A. Prevalence of hyperplasia and cancer in endometrial polyps in women with postmenopausal bleeding: a systematic review and meta-analysis. Post Reprod Health. 2019;25(2):86–94.
38. Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. J Minim Invasive Gynecol. 2009;16(4):465–71.
39. Timmermans A, Veersema S, Van Kerkvoorde T, Van Der Voet L, Opmeer B, Bongers M, et al. Should endometrial polyps be removed in patients with postmenopausal bleeding?—an assessment of study designs and report of a failed randomised controlled trial (ISRCTN73825127). BJOG Int J Obstet Gynaecol. 2009;116(10):1391–5.
40. Worldwide AAMIG. AAGL practice report: practice guidelines for the diagnosis and management of endometrial polyps. J Minim Invasive Gynecol. 2012;19(1):3–10.

Type I Endometrial Cancer: Early Stage

16

Robert E. F. Parker

Introduction

Endometrial cancer is a common gynaecological malignancy, with around 9000 new cases being diagnosed in the UK each year [1]. In England, age-standardized incidence was 29.1 per 100,000 population in 2019 [2]. Peak rates of endometrial cancer occur in the 75–79 year age group, and there is an upward trend in cases over time, with a 59% higher incidence now compared to the 1990s [1]. Endometrial cancers have long been divided into oestrogen-dependent type I, and the less common, clinically aggressive, oestrogen-independent type II [3]. Type I tumors comprise the large majority of endometrial cancers, are mostly endometrioid adenocarcinomas [3]. Type 1 cancers account for 80–90% of endometrial malignancies [4], and have a number of recognized risk factors, including obesity, diabetes, hypertension, polycystic ovarian syndrome (PCOS), nulliparity, and long term tamoxifen usage [5]. Rising rates of endometrial cancer are largely thought to be due to increasing rates of obesity [6]. Obesity results in unopposed oestrogen excess, insulin resistance and chronic inflammation [7]. In a number of cases, Type I endometrial cancers are thought to arise from pre-cancerous atypical endometrial hyperplasia, with a cumulative risk of cancer of 8% over 4 years in untreated women [8]. In addition, atypical hyperplasia has been associated with a rate of concomitant carcinoma of up to 43% in women undergoing hysterectomy [9]. Treatment for early stage type 1 cancers is usually surgical, with a total hysterectomy and bilateral salpingo-oophorectomy, although ovarian conservation can be considered in pre-menopausal patients with grade 1, stage 1A disease [10]. The molecular basis of endometrial cancer is being increasingly well understood, with implications for clinical management and the development of future treatments. For example, Mismatch Repair gene deficiency (MMRd) is linked to cases of endometrial cancer in patients with Lynch Syndrome, and is inherited in an autosomal dominant fashion [11]. However, loss of MMR can also occur spontaneously. Checking for specific molecular changes can help to guide whether further investigations, and referral to a genetics service is indicated. Other molecular drivers implicated in endometrial cancer include PTEN, p53, and BRCA 1 and 2 [10]. On basis of final histopathology and molecular classification, endometrial cancer is further classified as low risk, intermediate risk, high intermediate risk, high risk and metastatic (Fig. 16.1).

R. E. F. Parker (✉)
Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
e-mail: Robert.parker8@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_16

Risk group	2014 ESMO-ESGO-ESTRO Consensus	2020 ESGO-ESTRO-ESP Guidelines	
		Molecular classification unknown	Molecular classification known
Low	Stage IA endometrioid +low grade* +LVSI negative	Stage IA endometrioid + low-grade* + LVSI negative or focal	Stage I-II *POLE*mut endometrial carcinoma, no residual disease Stage IA MMRd/NSMP endometrioid
Intermediate	Stage IB endometrioid + low grade* + LVSI negative	Stage IB endometrioid + low-grade* + LVSI negative or focal Stage IA endometrioid + high-grade* + LVSI negative or focal Stage IA non-endometrioid** without myometrial invasion	Stage IB MMRd/NSMP endometrioid carcinoma + low-grade* + LVSI negative or focal Stage IA MMRd/NSMP endometrioid carcinoma + high-grade* + LVSI negative or focal Stage IA p53abn and/or non-endometrioid** without myometrial invasion
High-intermediate	Stage IA endometroid + high grade*, regardless of LVSI status Stage I endometrioid + low grade* + LVSI unequivocally positive, regardless of depth of invasion	Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion Stage IB endometrioid high-grade*, regardless of LVSI status Stage II	Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion Stage IB MMRd/NSMP endometrioid carcinoma high-grade*, regardless of LVSI status Stage II MMRd/NSMP endometrioid carcinoma
High	Stage IB endometrioid + high grade* regardless of LVSI status Stage II Stage III endometrioid with no residual disease Stage I-III non-endometrioid** with no residual disease	Stage III-IVA with no residual disease Stage I-IVA non-endometrioid** with myometrial invasion, and with no residual disease	Stage III-IVA MMRd/NSMP endometrioid carcinoma with no residual disease Stage I-IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease Stage I-IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced	Stage III with residual disease Stage IVA	Stage III-IVA with residual disease	Stage III-IVA with residual disease of any molecular type
Metastatic	Stage IVB	Stage IVB	Stage IVB of any molecular type

Fig. 16.1 ESMO-ESGO-ESTRO Consensus risk classification of endometrial cancer

Case 1: Atypical Endometrial Hyperplasia

Age, Parity	65 years P1+0; ECOG=1
Presenting complaints	Post menopausal bleeding × 7 months
Co morbidities	BMI = 32, hypertension
Gynaecological history	Previous cycles regular, normal periods. Previous smears regular and normal
Transvaginal sonography	Uterus normal size, endometrial thickness = 21 mm, bilateral adnexa normal
Endometrial biopsy	Atypical endometrial hyperplasia
MRI	Endometrium thickened 20 mm, no myometrial invasion seen Pelvic lymph nodes not enlarged, bilateral ovaries normal (Fig. 16.2)

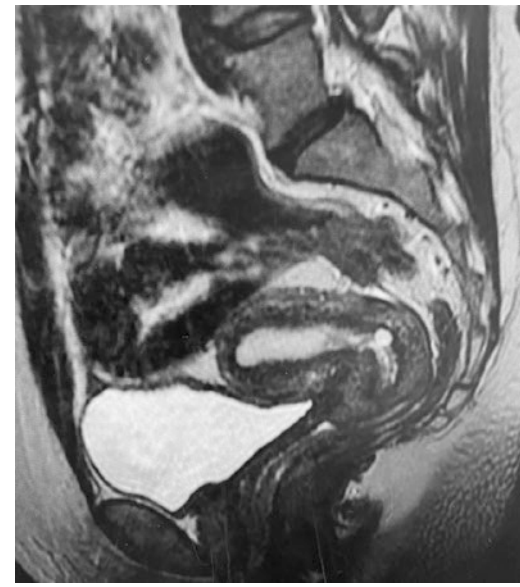


Fig. 16.2 Contrast enhanced MRI showing diffusely thickened endometrium 17 mm, no growth identified

Q. Classification of Endometrial Hyperplasia. Incidence of Cancer in Atypical Endometrial Hyperplasia?

As per Royal College of Obstetricians and Gynaecologist (RCOG) guidelines which is based on WHO classification - endometrial hyperplasia can be subdivided into 2 types based on presence or absence of cellular atypia. The two distinct groups of endometrial hyperplasia are: (1) hyperplasia without atypia or simple hyperplasia and (2) atypical hyperplasia (previously called complex hyperplasia with atypia) [12].

Endometrial hyperplasia without atypia will often undergo spontaneous regression [12]. The long-term risk of progression to cancer is less than 5%, and therefore management is usually medical with progesterone therapy with either systemic or local progesterone therapy with Mirena. Additional measures to improve aggravating factors like obesity, hyperinsulinemia or PCOS may need to be managed simultaneously to improve efficacy of hormone therapy [12].

Atypical hyperplasia is considered to be a precursor to endometrial cancer, and the risk of progression to cancer is thought to be 8% over 4 years, and 12.4% over 9 years [8]. It is difficult to understand for how long has the patient had the atypical hyperplasia for and co-existent cancer of endometrium is not uncommon.

Q. Does Atypical Hyperplasia on Endometrial Biopsy Require Hysteroscopic Evaluation of Endometrial Cavity?

Royal College of Obstetricians and Gynaecologists (RCOG) guidance states that diagnostic hysteroscopy should be considered to facilitate or obtain an endometrial sample, especially where outpatient sampling fails or is non-diagnostic [12]. Use of hysteroscopy for diagnosis of endometrial cancer does not upstage the disease; however low pressures should be used for the procedure.

If atypical hyperplasia is detected in an endometrial polyp, an endometrial biopsy should be obtained to sample the background endometrium [12]. If there is no background endometrial sampling available, hysteroscopy may be indicated, in order to enable further tissue sampling and allow excision of any residual polyp tissue.

If an adequate endometrial biopsy has confirmed the presence of atypical hyperplasia, hysteroscopy would not normally be required.

Q. Is There a Role of MRI Assessment in Atypical Hyperplasia?

MRI to aid the diagnosis of hyperplasia is not commonly used in UK practice [12], and is not thought to be helpful in identifying a malignant transformation [13, 14]. There are no data to support the routine use of MRI or CT during follow-up for atypical hyperplasia [12]. As there is a high incidence of co-existence of endometrial cancer with atypical hyperplasia, there may be a role of MRI in women who are having fertility preserving or non-surgical treatment of their atypical hyperplasia. In older women who are having hysterectomy for atypical hyperplasia then there is no proven benefit of MRI assessment as any associated cancers with atypical hyperplasia tend to be type 1 and early stage.

Q. What Is the Management of Atypical Hyperplasia?

- Standard treatment for atypical hyperplasia is a total hysterectomy, due to the risk of underlying malignancy and/or progression to cancer. In peri- or post-menopausal patients, bilateral salpingo-oophorectomy should also be performed, due to the risk of underlying malignancy [12].
- Laparoscopic hysterectomy is preferred because it is associated with a shorter hospital stay, less postoperative pain and a quicker recovery than open surgery [12]. In patients who decline surgery, or are considered unfit due to comorbidities, hormonal treatment and follow up with repeated endometrial biopsies can be considered.
- In younger premenopausal women with atypical hyperplasia, there is a role of fertility pres-

ervation in women desirous of future pregnancy. Mirena or oral progestogens are equally effective. In younger premenopausal women (<40 Years) requiring hysterectomy for atypical hyperplasia either because of heavy bleeding or not desirous of future pregnancy, can be given option of preserving the ovaries to avoid premature surgical menopause.

Case 1

Underwent Total laparoscopic hysterectomy + bilateral salpingo-oophorectomy

HPE: Gross: Polypoidal tumor in endometrial cavity

Grade 1 endometrioid adenocarcinoma, <50% myometrial invasion, CK7 +ve, WTI−ve,

ER, PR positive, P16 negative, LVSI negative, MMR-proficient

FIGO stage IA grade 1

Q. Further Management and Follow Up Protocol?

The risk of recurrence after hysterectomy in patients diagnosed with grade 1, stage 1A1 endometrioid adenocarcinoma is considered to be low. Recurrence rates are less than 5% over 5 years, with 5 year disease-specific survival as high as 97.3% in one study [15].

Adjuvant treatment is not recommended for these low risk endometrial cancers [10], and patients can be offered patient initiated follow up, where appropriate.

Case 2: Endometrial Cancer Stage 1B

Age, parity	43 years P2+0; ECOG = 1; BMI = 28
Presenting complaints	Post menopausal bleeding × 7 months
Co morbidities	Nil
Gynaecological history	Previous cycles regular, normal periods. Previous cervical smears regular& normal
Transvaginal sonography	Uterus normal size, endometrial thickness = 21 mm, bilateral adnexa normal
Endometrial biopsy	Well differentiated endometrioid cancer
MRI	Endometrial cavity growth with >50% myometrial invasion, no cervical stromal involvement, no pelvic or retroperitoneal lymphadenopathy
Surgery	TLH + BSO (Fig. 16.1)
Histopathology	Grade 1 endometrioid adenocarcinoma, >50% myometrial invasion, lymphovascular space invasion+, no microscopic involvement of adnexa or cervical stroma ER+ve, PR−ve, loss of MSH 2

Q. Role of Lymph Node Assessment in Early Stage Endometrial Cancer?

Data from the 2009 ASTEC trial showed that there was no benefit in terms of overall or recurrence-free survival for systematic pelvic lymphadenectomy in women with stage 1 endometrial cancer [16]. This study has been questioned about the surgical quality and adequacy of lymph node sampling in this trial. There was no distinction in this study between low risk, intermediate and high risk endometrial cancers undergoing lymphadenectomy. We do know there is a higher incidence of pelvic nodal metastasis in high risk group or even high intermediate group associated with LVSI. We know from PORTEC 2 trial there is a benefit from avoiding external beam radiotherapy and support vaginal vault brachytherapy in intermediate risk group [17]. We also know from PORTEC 3 trial that there is a benefit of treating node positive endometrial cancer with adjuvant chemotherapy + radiotherapy [18].

So ASTEC has made us conscious about blindly performing pelvic lymphadenectomy in all early stage endometrial cancer is not beneficial but causes harm. However, in intermediate and high risk group it is important to analyse the

pelvic nodes for metastasis to be able to plan the adjuvant treatment accordingly, which is, spare external beam radiotherapy in node negative high risk endometrial cancers and to give chemotherapy and radiotherapy for node positive intermediate and high risk endometrial cancers (PORTEC 3). So we understand lymph node assessment is essential for analyzing lymph node metastasis and for planning of adjuvant treatment.

Systematic pelvic lymphadenectomy has its associated morbidity and this is increasingly being replaced by sentinel node assessment. Sentinel node is the first node to which cancer is likely to spread from the primary tumor. The incidence of sentinel lymph nodes according to the depth of myometrial invasion and grade of tumor is shown in Table 16.1 [19]. The use of sentinel lymph node biopsy (SLNB), rather than systematic pelvic lymphadenectomy has been shown to have a high negative predictive value [10].

The advantages of SLNB include a reduced risk of lymphoedema compared with standard lymphadenectomy, and increased detection of positive nodes as helps in identifying nodes in unusual sites like sacral nodes, lower paraaortic also ultrastaging of sentinel lymph nodes identifies more micro metastasis than normal lymph node assessment. Newer surgical techniques for detection of SLNB are being used. Blue dye and technetium scanning replaced by ICG (indocyanine green) infrared detection of nodes. Developments in analysis of sentinel nodes undergoing developments from H&E staining to ultrastaging and now OSNA (One-step nucleic acid amplification) method is an increasingly used procedure for intraoperative analysis of sentinel lymph node (SLN) status

Table 16.1 Incidence of sentinel lymph nodes depending on the grade and depth of invasion in early stage endometrioid endometrial cancer [19]

Depth of myometrial invasion	Grade 1	Grade 2	Grade 3
Non invasive	Nil	N	3.5%
< 50%	4.5%	4%	3%
>50%	10%	20%	24%

- This could help guide planning and decision making regarding adjuvant radiotherapy [10].
- Sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease [20]

Q. Discuss Prognostic Risk Groups of Endometrial Cancers?

Now molecular profiling is increasingly being incorporated in reporting of early stage endometrial cancer to obtain a prognosis and formulate their adjuvant treatment. All early stage endometrial cancers have their mismatch repair genes tested along with immunohistochemistry for P53 (positive if null/aberrant, negative if wild type), estrogen and progesterone receptor (ER/PR) status. Apart from low risk category all patients with endometrial cancer of intermediate and high risk group also have their POLE testing and they are divided into 4 different categories based on their molecular profiling. The 2016 risk stratification has been modified in 2021 to incorporate the molecular profiling of the endometrial cancer.

In the above patient's case, the findings on final histology were of a grade 1, stage 1B cancer (>50% myometrial invasion) with lymphovascular space invasion (LVSI), but no spread to the adnexa or cervix. The loss of MSH2 (mismatch repair protein) status is considered an adverse prognostic factor.

According to the 2020 ESGO guidelines, as shown in Fig. 16.1, this particular patient would be classified as "High-intermediate" risk, in view of the LVSI and mismatch repair deficiency [20]. She would benefit from POLE testing and if POLE negative then adjuvant external beam and vaginal vault brachytherapy. However, if POLE test was positive then there maybe a case of avoiding adjuvant radiotherapy, However, no randomized trial have been conducted so far, to support the confidence of avoiding adjuvant treatment in POLE positive results. This case in hindsight could have benefited from SLNB as

that could have avoided the need for adjuvant external beam radiotherapy if the SLNB was negative.

The four molecular subtypes of endometrial cancer are *POLE*-ultramutated (*POLE*mut), MMR-deficient (MMRd), or no specific molecular profile (NSMP), p53 abnormal (p53abn).

BGCS & BAGP (British Society of Gynaecological Oncologist and British socity of Gynaecological Pathologist) have set an algorithm for molecular profile testing of endometrial cancer which has been adopted currently in UK clinical practice (Fig. 16.3).

Q. Discuss Adjuvant Therapy for This Case

In view of the prognostic features described, i.e. stage IB, low-grade endometrioid cancer with LVSI, adjuvant treatment would be recommended [20]. In this patient's case, lymph node sampling was not performed. Therefore, ESGO guidelines would recommend adjuvant External Beam Radiotherapy, rather than just vaginal brachytherapy [20]. ESGO guidelines also suggest that chemotherapy may be considered in this case. However, in stage I-II disease this

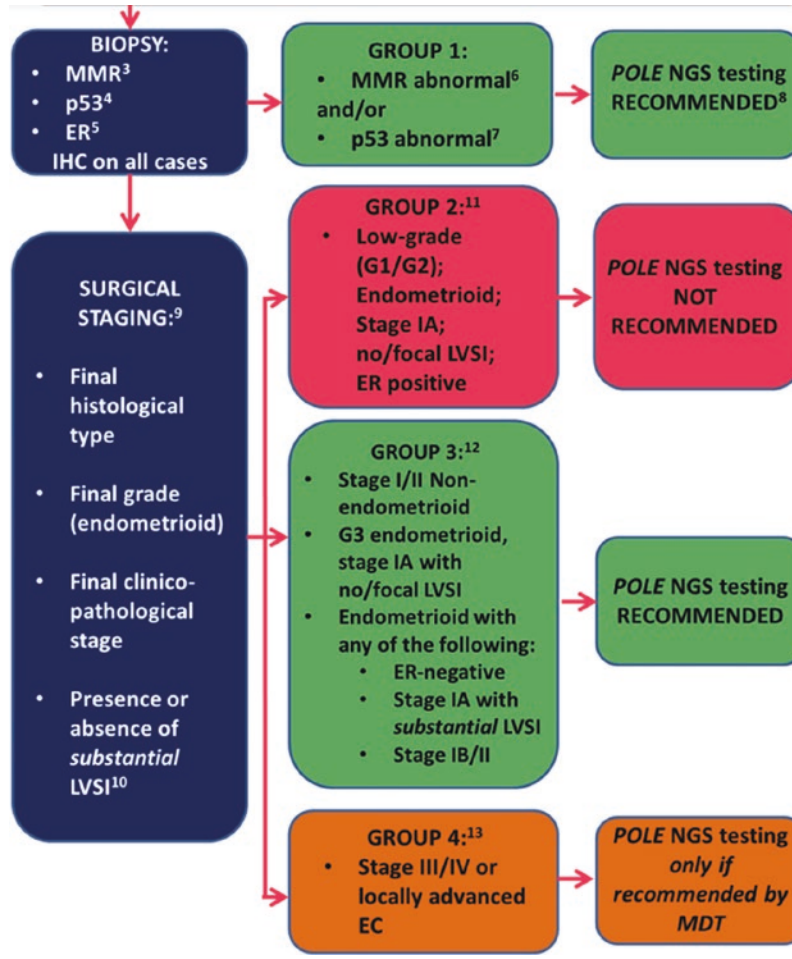


Fig. 16.3 BAGP and BGCS guidelines for Molecular profile testing of endometrial cancer in UK (April 2022) [21]

should be a multi-disciplinary shared decision, in view of the potential for toxicity from chemotherapy [20].

British Gynaecological Cancer Society (BGCS) guidance recommends clinic-based follow up for 5 years for patients with high-intermediate risk cancers, followed by Patient Initiated Follow up [10].

Q. Can Adjuvant Treatment Be Tailored According to the Molecular Classification of Endometrial Cancer

In future, clinicians may be able to incorporate individualised genetic information into their clinical care, enabling tailored treatment for endometrial cancer [10]. For example, recent ESGO guidance has endorsed considering limiting adjuvant therapy in stage II cancers which show the *POLEmut* mutation, as these have an excellent prognosis compared with other subtypes [20]. The ongoing PORTEC-4a study may provide more definitive data on adjuvant treatment options in stage I and II cancers, based on their individual molecular profiles [10].

Case 3: Endometrioid Cancer Medically Unfit

Age, parity	85 Years, nulliparous; ECOG = 3; BMI = 38
Presenting complaints	Post menopausal bleeding
Co morbidities	Ischemic heart disease, hip replacement walks with a stick
TVS	Uterus bulky bulky uterus ET = 14 mm, adnexa normal
Endometrial biopsy	Grade 1 endometrioid cancer
MRI	Endometrial cavity growth with <50% myometrial invasion, no cervical stromal involvement, no pelvic or retroperitoneal lymphadenopathy
Surgical fitness	Unfit for surgery, very high risk

Q. Further Management in This Case?

Patients with significant medical comorbidities may not be candidates for standard treatment with total hysterectomy (laparoscopic or open), and alternative treatment options can be considered. Assessment of fitness for surgery should ideally be carried out at a centre with specialist anaesthetic experience in managing high-risk patients [20]. ESGO and BGCS guidelines suggest that vaginal hysterectomy may be considered for women who cannot undergo abdominal or minimal access hysterectomy [10, 20].

In patients who are considered too high risk for surgical intervention, intra-cavitary brachytherapy may be considered for low grade, stage I tumours without deep myometrial invasion [10]. In higher grade tumours, or tumours with deep myometrial invasion, brachytherapy can be combined with external beam radiation therapy [10, 20].

Hormonal treatment can also be considered for patients where surgery or radiotherapy is not possible, or where such treatments are unacceptable to the patient. It can also be used to postpone surgical treatment, in patients who may regain fitness, or where access to high dependency or intensive care is limited, for example, as during the COVID-19 pandemic [10].

Medical treatment is usually with progesterone, and is similar to hormonal treatment used in younger patients who wish to preserve their fertility. Treatments include medroxyprogesterone acetate, megestrol acetate, and/or a levonorgestrel-releasing intrauterine system [10].

Discussions regarding treatment options should take place in the context of an expert multi-disciplinary team [22].

Case 4: Endometrial Cancer with Morbid Obesity

Age, parity	75 Years, P1+0; ECOG = 3; BMI = 70
Presenting complaints	Post menopausal bleeding

Co morbidities	Morbid obesity with obstructive sleep apnea
TVS	Uterus bulky, 1 × 2 cm growth in endometrial cavity, no myometrial invasion adnexa normal
Endometrial biopsy	Grade 1 endometrioid cancer
MRI	Endometrial cavity growth 2 cm with no myometrial invasion, no cervical stromal involvement, no pelvic or retroperitoneal lymphadenopathy
Surgical fitness	Unfit for surgery, very high risk

Q. Discuss the Management

Obesity is a major risk factor for endometrial cancer, and every 5 kg/m^2 increase in body mass index (BMI) confers a 1.6-fold higher risk of cancer [23]. Morbid obesity can often preclude surgery due to high operative and peri-operative risks [17].

As discussed in Case 3 (above), hormonal or radiotherapy treatment may be considered where surgery is not feasible.

- In this patient's case, there is a grade 1 cancer, with no myometrial invasion, local spread or lymphadenopathy on MRI.
- Intracavitary brachytherapy would therefore be an option for the multidisciplinary team to consider [10]. Hormonal treatment with progesterone would be another option, as discussed in Case 3.

Where facilities and expertise allow, robotic surgery can be offered to super morbidly obese patients with endometrial cancer [24, 25], and may facilitate completion of minimally invasive hysterectomy. Depending on the availability of robotic surgery, this might be a potential treatment option, following specialist pre-operative assessment.

Weight loss treatment and bariatric surgery have been shown to reduce the risk of developing endometrial cancer [26, 27]. However, there had been insufficient evidence regarding the effects of significant weight loss in women with a history of endometrial cancer, compared to those receiving usual care [28].

Research is ongoing into the role of weight loss on obesity-associated atypical hyperplasia and early stage cancer of the endometrium [29, 30]. Recent evidence suggests that weight loss may improve oncological outcomes in women with obesity-associated endometrial neoplasia treated with progestins [30].

Key Points

1. The incidence of endometrial cancer is projected to continue to increase in the UK.
2. Increases in endometrial cancer rates have also been observed in many other countries, especially those undergoing rapid socioeconomic transition. Type 1 endometrial cancers are therefore likely to remain a major part of the workload for gynaecological oncology teams in the future.
3. Advances in management, including targeted or tailored treatments, may enable more individualized care, but might also add complexity to adjuvant treatment decisions, emphasizing the importance of multidisciplinary decision making.
4. Addressing modifiable risk factors for type 1 endometrial cancers, in particular the obesity epidemic, is likely to be an ongoing challenge for healthcare systems.
5. Future research into prevention, screening, diagnosis and treatment may help guide improvements in care.

References

1. Cancer Research UK: Uterine incidence statistics. [Online] Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence. Accessed 29 Mar 2022.
2. NHS digital: cancer registration statistics, England 2019. [Online] Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2019/content. Accessed 29 Mar 2022.
3. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, Wolk A, Wentzensen N, Weiss NS, Webb PM, van den Brandt PA, van de Vijver K, Thompson PJ, Australian National Endometrial Cancer Study Group, Strom BL, Spurdle AB, Soslow

RA, Shu XO, Schairer C, Sacerdote C, Rohan TE, Robien K, Risch HA, Ricceri F, Rebbeck TR, Rastogi R, Prescott J, Polidoro S, Park Y, Olson SH, Moysich KB, Miller AB, McCullough ML, Matsuno RK, Magliocco AM, Lurie G, Lu L, Lissowska J, Liang X, Lacey JV Jr, Kolonel LN, Henderson BE, Hankinson SE, Håkansson N, Goodman MT, Gaudet MM, Garcia-Closas M, Friedenreich CM, Freudenheim JL, Doherty J, De Vivo I, Courneya KS, Cook LS, Chen C, Cerhan JR, Cai H, Brinton LA, Bernstein L, Anderson KE, Anton-Culver H, Schouten LJ, Horn-Ross PL. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31(20):2607–18. https://doi.org/10.1200/JCO.2012.48.2596. Epub 2013 Jun 3. PMID: 23733771; PMCID: PMC3699726.

4. Saso S, Chatterjee J, Georgiou E, Ditri AM, Smith JR, Ghaem-Maghami S, et al. Endometrial cancer. BMJ. 2011;343:d3954. https://doi.org/10.1136/bmj.d3954.
5. Acheson N, Luesley D. Gynaecological oncology for the MRCOG and beyond. 2nd ed. London: RCOG Press; 2010. p. 4–5.
6. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and endometrial cancer. 2018.
7. Mackintosh ML, Crosbie EJ. Obesity-driven endometrial cancer: is weight loss the answer? BJOG. 2013;120(7):791–4.
8. Lacey JV Jr, Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. J Clin Oncol. 2010;28:788–92.
9. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106:812–9.
10. Morrison JB, Buckley L, Clamp A, Crosbie E, Drew Y, Durrant L, Forrest J, Fotopoulou C, Gajjar K, Ganesan R, Gupta J, Hughes J, Miles T, Moss E, Nanthakumar M, Newton C, Ryan N, Walther A, Taylor A. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: recommendations for practice. Eur J Obstetr Gynecol Reproduct Biol. 2022;270:50–89.
11. Crosbie EJ, Ryan NAJ, Arends MJ, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21(10):2390–400.
12. Gallos ID, Alazzam M, Clark TJ, Faraj R, Rosenthal AN, Smith PP, Gupta JK. Management of endometrial hyperplasia (green-top guideline No. 67). Royal College of Obstetricians and Gynaecologists. [Online] Available from: www.rcog.org.uk/media/knmjbj5c/gtg_67_endometrial_hyperplasia.pdf. Accessed 18 May 2022.
13. Ofinran O, Balega J. The value of magnetic resonance imaging in investigating complex atypical hyperplasia of the endometrium. Minerva Ginecol. 2016;68(4):400–4. Epub 2016 Mar 22. PMID: 27002383.
14. Natarajan P, Vinturache A, Hutson R, Nugent D, Broadhead T. The value of MRI in management of endometrial hyperplasia with atypia. World J Surg Oncol. 2020;18(1):34. https://doi.org/10.1186/s12957-020-1811-5. PMID: 32041614; PMCID: PMC7011375.
15. Lajer H, Elnegaard S, Christensen RD, Ortoft G, Schledermann DE, Mogensen O. Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey. Acta Obstet Gynecol Scand. 2012;91(8):976–82. https://doi.org/10.1111/j.1600-0412.2012.01438.x. Epub 2012 Jun 18. PMID: 22548255.
16. ASTEC Study Group, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet (London, England). 2009;373(9658):125–36. https://doi.org/10.1016/S0140-6736(08)61766-3.
17. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. PORTEC Study Group. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816–23.
18. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. PORTEC study group. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295–309.
19. Mueller JJ, Nobre SP, Braxton K, Alektiar KM, Leitao MM Jr, Aghajanian C, Ellenson LH, Abu-Rustum NR. Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma. Gynecol Oncol. 2020;157(3):619–23.
20. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 31(1):12–39. https://doi.org/10.1136/ijgc-2020-002230.
21. National Institute for Health and Care Excellence. Testing strategies for lynch syndrome in people with endometrial cancer. Diagnostics guidance Published: 28 October 2020. www.nice.org.uk/guidance/dg42.
22. NHS standard contract for complex gynaecology - specialist gynaecological cancers. Schedule 2- The Services A. Service Specifications. In: NHS England, editor. 2013.
23. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement

therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomark Prev. 2010;19:3119.
24. Stephan JM, Goodheart MJ, McDonald M, Hansen J, Reyes HD, Button A, Bender D. Robotic surgery in supermorbidly obese patients with endometrial cancer. Am J Obstet Gynecol. 2015;213(1):49.e1–8. https://doi.org/10.1016/j.ajog.2015.01.052. Epub 2015 Jan 30. PMID: 25644437.
25. Cusimano MC, Simpson AN, Dossa F, Liani V, Kaur Y, Acuna SA, Robertson D, Satkunaratnam A, Bernardini MQ, Ferguson SE, Baxter NN. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 2019;221(5):410–428.e19. https://doi.org/10.1016/j.ajog.2019.05.004. Epub 2019 May 10. PMID: 31082383.
26. Anveden A, Taube M, Peltonen M, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish obese subjects study. Gynecol Oncol. 2017;145(2):224–9.
27. Luo J, Chlebowski RT, Hendryx M, et al. Intentional weight loss and endometrial Cancer risk. J Clin Oncol. 2017;35(11):1189–93.
28. Kitson S, Ryan N, MacKintosh ML, Edmondson R, Duffy JMN, Crosbie EJ. Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Cochr Datab Syst Rev. 2018;(2):CD012513. https://doi.org/10.1002/14651858.CD012513.pub2. Accessed 21 May 2022.
29. Naqvi A, MacKintosh ML, Derbyshire AE, et al. The impact of obesity and bariatric surgery on the immune microenvironment of the endometrium. Int J Obes. 2022;46:605–12. https://doi.org/10.1038/s41366-021-01027-6.
30. Barr CE, Ryan NAJ, Derbyshire AE, Wan YL, MacKintosh ML, McVey RJ, Bolton J, Fitzgerald C, Awad D, Slade RJ, Syed AA, Ammori BJ, Crosbie EJ. Weight loss during intrauterine progestin treatment for obesity-associated atypical hyperplasia and early-stage cancer of the endometrium. Cancer Prev Res (Phila). 2021;14(11):1041–50. https://doi.org/10.1158/1940-6207.CAPR-21-0229. Epub 2021 Aug 4. PMID: 34348914.

17 Type I Endometrial Cancer: Advanced Stage

Sarada Kannangara

Introduction

Endometrial adenocarcinoma is the most common gynaecological cancer in western world [1]. Type one or endometrioid type is the commonest accounting for 80% of endometrial carcinomas The risk factors include obesity, nulliparity, hypertension, diabetes mellitus, tamoxifen therapy [2] Advanced endometrial cancers are Stage III and IV and account for 8–12% of the endometrial carcinoma, however the shows significantly less 5 year survival rate. (22% in stage IV disease) [3, 4].

Surgical resection remains mainstay of management of endometrial carcinoma, even in advanced stage. Moreover, the use of adjuvant radiotherapy and chemotherapy proven to have survival benefits at advanced stage. Therefore, multidisciplinary team lead multimodal therapy stays as the standard management of advanced endometrial carcinoma [4].

Most of randomized studies were performed in early stage of endometrial cancers, hence the studies assessing the late stage disease are very sparse. This is because, majority of endometrial carcinomas are present in very early stage, there-

S. Kannangara (✉)
Pan Birmingham Gynecologic Oncology Centre, Birmingham, UK

National Cancer Institute, Maharagama, Sri Lanka

Teaching Hospital Mahamodara-Galle, Galle, Sri Lanka

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_17

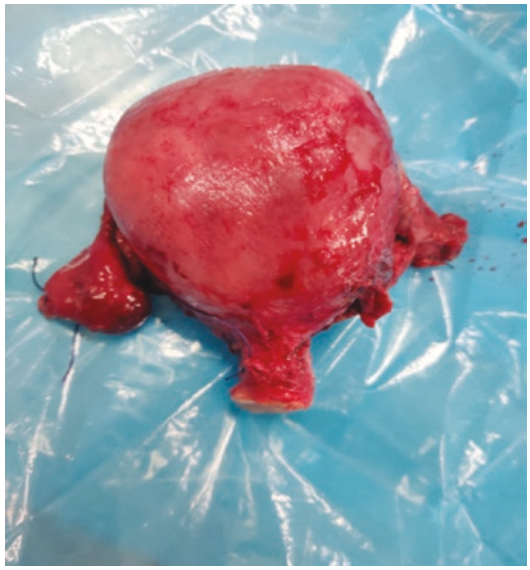


Fig. 17.1 Large bulky uterus filled with tumour

fore large cohorts of patients are available for, research in early endometrial carcinoma. Moreover, the excellent survival rates in timely intervention at early stage drag more researchers to study primarily on early stage endometrial carcinoma. This is in contrast to ovarian cancers where most of the studies are on advanced stage disease. Therefore, most of the conclusions are based on assessing the outcome of advanced disease at larger studies. This chapter will discuss the case scenarios of advanced endometrioid cancer (Fig. 17.1).

Case 1: Endometrioid Carcinoma with Omental Metastasis

Age, Parity	51 Years, P2+0; ECOG = 0; BMI = 27
Presenting complaints	Post menopausal bleeding
Co morbidities	Chronic hypertension
TVS	6 × 7 cm growth in endometrial cavity, >50% myometrial invasion adnexa normal
Endometrial biopsy	Grade 1 endometrioid cancer
CECT abdomen pelvis	6.2 × 4.6 × 7.8 cm enhancing lesion, lymph nodes negative
MRI	73 × 54 × 64 mm soft tissue mass, >50% myometrial invasion, no cervical stromal invasion no pelvic or retroperitoneal lymphadenopathy
Surgery	Total abdominal hysterectomy + bilateral salpingo oophorectomy + pelvic and para aortic lymphadenectomy with supracolic omentectomy
Intraoperative findings	Uterus 10 weeks size. R tube and ovary normal. Left tube and ovary buried in adhesions. Pelvic and paraaortic lymph nodes enlarged. **Omental nodule 2 × 3 cm**
Histopathology	Endometroid carcinoma, FIGO grade 3, 7.5*6.5*2.3 cm Myometrial invasion: >50%, uterine serosa involvement: Not identified Cervical stroma involvement present Omentum shows multiple tumor deposits LVSI absent Regional lymph nodes: Right pelvic lymph nodes-0/25, left pelvic lymph nodes 0/11; Para aortic lymph nodes- 0/17 IHC: p53 negative, MMR proficient FIGO stage: Stage IVB;pT2 pNoM1

Indications of Systematic Lymphadenectomy in Endometrial Cancer? What Are the Indications of Para Aortic Lymphadenectomy?

Overall there is no statistically significant results on available studies to support lymphadenectomy in early, advanced or recurrent disease in terms of overall survival rates. However, lymphadenectomy provides better staging and more tailored made therapy for advanced and high grade cancers [5]. Therefore, it is recommended in high level of suspicion of lymph node disease. Paraaortic lymphadenectomy is indicated if there is radiological evidence of extra uterine disease [6, 7]. Patients who got positive lymph nodes removed, had better recurrence free survival [8].

Q. What Is Incidence of Microscopic and Macroscopic Omental Involvement in Endometrial Cancer? What Are the Indications of Routine Omentectomy in Endometrial Cancer?

Omental involvement falls under the category of distant metastasis and therefore FIGO staging will be IVB. 6–8.3% of microscopic omental deposits found in the endometrial cancers where the local disease is confined to the uterus [9, 10]. Although there is no evidence to evaluate the value of omentectomy in grade 1 disease, there is sufficient evidence to recommend the omentectomy in grade 3 and serous endometrial carcinomas, even the local disease is confined to uterus or primary tumour has spread to adenexa [11]. Omentectomy should also be performed in undifferentiated carcinoma and carcinosarcomas. It can be omitted in clear cell cancer.

How Much Sampling Is Adequate for Microscopic Examination? Should It Be an Omental Biopsy, an Infracolic Omentectomy, or a Total Omentectomy?

Since there is visible multiple omental deposits, total ometectomy is recommended, however if there were no visible deposits infracolic or 15 × 10 cm size sample is adequate [11].

Q. What Are the High Risk Factors Associated with Omental Metastasis

The range of omental metastasis varies across histological subtypes. However, non endometriod types has higher risk of omental metastasis [11, 12]. Extra uterine spread of primary tumour, grade 3 endometriod type also increases the risk of omental metastasis of endometrial carcinoma [13] Serous subtype has the highest incidence and European consensus recommend omentectomy only for serous subtype [14] (Fig. 17.2).

Fig. 17.2 Omental nodules in carcinoma endometrium

Q. Prognosis and Adjuvant Treatment?

FIGO stage IV, 5 year survival rate in general is 22% [4], However, several factors influence the overall prognosis. The comprehensive discussion of multidisciplinary team and individualized adjuvant treatment has a vital role to play. Combined chemo and radiotherapy has used with promising results, and there are some evidence to suggest whole abdominal radiotherapy also as adjuvant treatment [15, 16]. In GOG 122 study it showed that chemotherapy combined with radiotherapy has better survival rate in stage IV endometrial cancers [17], However, recent meta-analysis shows results that radiotherapy alone had better survival rates. However, the analysis has not taken the level of surgical cyto-reduction into account in the interpretation, therefore still treating systemic disease with chemotherapy is advisable [18, 19].

Case 2

Age, Parity	**52 Years, Nulliparous**; ECOG = 1; BMI = 35
Clinical presentation: Post menopausal bleeding Co morbidities: Type 2 diabetes mellitus (controlled on oral hypoglycaemics) Endometrial biopsy: Moderately differentiated endometrioid cancer PET CT scan: Heterogenous enhancing lesion with internal necrosis (8.9*6.6*10.3 cc) in endometrial cavity & cervix. Multiple exophytic lesion in uterus, largest 3.2*2.5 cm. No parametrial extension. Mild FDG uptake in b/l axillary areas MRI: 8 × 6 cm growth, extending into endocervical canal with stromal invasion. Myometrial invasion>50%. **Patient lost to follow up due to COVID-19 lockdown**	
Presented after 1.5 years	C/O irregular vaginal bleeding and heaviness lower abdomen Examination: Uterus 12 weeks soft and broad, cervix hard infiltrative, nodular, growth felt at the external os. Left parametrium minimal nodular thickening
Trans vaginal sonography	Growth in the endometrium extending to the cervix, collection 3 cm at the fundus, very thinned out myometrium, serosa intact
PET CT scan (additional findings compared to previous one)	• Large enhancing mass in endometrium and cervix • Bilateral hilar and perioesophageal lymph nodes avid? Metastasis • Mediastinal lymph nodes avid uptake +

Q. Further Management?

The patient needs multimodal treatment as there are clear evidence of disease spread beyond abdomen. Surgical management is the mainstay even though complete removal of all metastasis, specially from the chest is not feasible. Surgical debluking includes modified radical hysterectomy pelvic and para-aortic lymph node removal, omentectomy and removal of all possible disease, which needs to be followed up by pelvic radiotherapy and chemotherapy [20]. In metastatic endometrioid type tumours, there may be a place of endocrine therapy with progestageons. Anti HER-2 therapy can be used, however it is more significant for serous tumors [21, 22].

Q. Role of Upfront Surgery Versus Neo-Adjuvant Chemotherapy Followed by Surgery?

The decision for neo-adjuvant chemotherapy has to be taken balancing the ability of the patient of that of a surgical undertaking [23]. Since the patient is young and able tolerate extensive surgery she was offered upfront surgery and adjuvant chemotherapy and radiotherapy. However, if the patients physical condition hampered the advanced gynae-oncology surgery, there is an option of neo-adjuvant chemotherapy and simple hysterectomy BSO later.

Q. Prognosis?

The prognosis of stage IV disease is much better with adjuvant chemotherapy [19] However, overall 5 year survival rate is about 22%.

Case 3

Age, Parity	60 Years, P1+0; ECOG = 1; BMI = 32
Presenting complaints	Post menopausal bleeding
Co morbidities	Nil
Transvaginal ultrasound	2 × 3 cm growth in endometrial cavity, >50% myometrial invasion adnexa normal
Endometrial biopsy	Grade 3 endometrioid adeno carcinoma
MRI abdomen and pelvis	2.5 × 3 × 2.8 cm soft tissue mass in uterine cavity, >50% myometrial invasion, cervical stromal invasion present, left external and internal iliac nodes 1.5 cm enlarged suggestive of metastasis. Multiple preaortic, interaortocaval and Para aortic nodes 8 mm-1 cm near the left renal artery+

Q. What Further Investigative Work Up Should Be Done in This Case?

The mainstay of managing advanced stage endometrial carcinoma is accurate staging, since this is a grade 3, CT chest abdomen and pelvic will give more details about mediastinal lymph nodes and if there any omental deposits.

Omental micrometastasis plays vital prognostic factor even at early stage, increased CA- 125 levels has value in predicting, microscopic omental disease [13].

PET scan will gather more information about the chest, if there is suspicious lesions in contrast enhanced CT scan.

Q. Further Management?

Surgery remains first line option in any stage of endometrial carcinoma if patient is physically fit and willing to undergo surgery. When there is obvious disease out side the uterus, pelvic and para-aortic lymphadenectomy not only have staging purpose, but also therapeutic value in cytoreduction [24], adequate omental biopsy for detention of micro-metastasis is important in accurate staging of the disease.

The patient underwent upfront surgery with Total abdominal hysterectomy + bilateral salpingo oophorectomy + bilateral pelvic lymphadenectomy + removal of enlarged para aortic nodes.
Final histology: grade 3 endometrioid carcinoma stage III C2.

Q. Prognosis and Adjuvant Treatment?

In the absence of omentectomy and chest imaging, there is a possibility of understaging the disease of this patient. However, there is no difference in adjuvant therapy as combined chemotherapy and radiotherapy is the treatment of choice [25]. Radiotherapy includes both external beam pelvic radiotherapy and vaginal brachytherapy [26]. Chemotherapy regimens include Carboplatin, paclitaxel, doxorubicin, cisplatin that are used as single agent or in combination, depend on unit guidelines and MDT discussions [25, 27–29].

However, overall 5 year survival rate is about 27% in stage IIIC disease [30].

Conclusions and Key Points

1. Multidisciplinary patient base approach has the best curative chance for the patient
2. Surgery remains mainstay of management even in advance disease
3. Complete cyto-reductive surgery should be the aim, – include hysterectomy +BSO, pelvic and para-aortic lymph node dissection and omentectomy.
4. Combined adjuvant chemotherapy and radiotherapy have better survival rate than radiotherapy alone
5. New modalities of treatment are in the verge including anti HER-2 therapy, immunotherapy, anti-angiogenic therapy

References

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int J Cancer. 2005;117(1):123–31.
2. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, Gabra H, Paraskevaidis E, Martin-Hirsch P, Tsilidis KK, Kyrgiou M. Risk factors for endometrial cancer: an umbrella review of the literature. Int J Cancer. 2019;145(7):1719–30.
3. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491–505.
4. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician. 2016;93(6):468–74.
5. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2012;120(2 Pt 1):383–97.
6. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2017;10(10):CD007585.
7. Aalders JG, et al. Endometrial cancer—revisiting the importance of pelvic and Para aortic lymph nodes. Gynecol Oncol. 2007;104(1):222–31.

8. Swift BE, Philp L, Atenafu EG, Malkani N, Gien LT, Bernardini MQ. Lymphadenectomy for high-grade endometrial cancer: does it impact lymph node recurrence? Eur J Surg Oncol. 2022;48(5):1181–7.
9. Demirkiran F. Controversies in the management of endometrial cancer 2012. Open J Obstet Gynecol. 2012;02(04):373–81.
10. Joo WD, Schwartz PE, Rutherford TJ, Seong SJ, Ku J, Park H, et al. Microscopic omental metastasis in clinical stage I endometrial cancer: a meta-analysis. Ann Surg Oncol. 2015;22(11):3695–700.
11. Bayrak M, Yılmaz A, Yılmaz F, İlhan O, Oz Atalay F, Ozan H. Omental micrometastasis in endometrial cancer. Oncol Res Treat. 2019;42(9):466–9.
12. Turan T, Ureyen I, Karalök A, Taşçı T, Ilgın H, Keskin L, Kose MF, Tulunay G. What is the importance of omental metastasis in patients with endometrial cancer? J Turk Ger Gynecol Assoc. 2014;15(3):164–72.
13. Kaban A, Topuz S, Erdem B, Sozen H, Numanoğlu C, Salihoğlu Y. Is Omentectomy necessary for non-Endometrioid endometrial cancer. Gynecol Obstet Investig. 2018;83(5):482–6.
14. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Int J Gynecol Cancer. 2016;26(1):2–30.
15. Bruzzone M, Miglietta L, Franzone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV endometrial cancer patients. Gynecol Oncol. 2004;93(2):345–52.
16. Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley HD, Malfetano JH, Mychalczak BR, King ME. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a gynecologic oncology group study. Gynecol Oncol. 2005;97(3):755–63.
17. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006;24:36–44.
18. Rajkumar S, Nath R, Lane G, Mehra G, Begum S, Sayasneh A. Advanced stage (IIIC/IV) endometrial cancer: role of cytoreduction and determinants of survival. Eur J Obstet Gynecol Reprod Biol. 2019;234:26–31.
19. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, DiSilvestro P, Pearl ML, Argenta PA, Powell MA, Zweizig SL, Warshal DP, Hanjani P, Carney ME, Huang H, Cella D, Zaino R, Fleming GF. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG oncology/GOG0209). J Clin Oncol. 2020;38(33):3841–50.
20. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, Tatebe K, Veneris JL. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019;69(4):258–79.
21. Singh M, Zaino RJ, Filliaci VJ, Leslie KK. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2007;106:325–33.
22. Soumerai TE, Donoghue MTA, Bandlamudi C, et al. Clinical utility of prospective molecular characterization in advanced endometrial cancer. Clin Cancer Res. 2018;24:5939–47.
23. Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, Neven P, Moerman P, Vergote I, Amant F. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer. 2009;101(2):244–9.
24. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol. 2010;118:14–8.
25. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19:295–309.
26. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375:816–23.
27. Matei D, Filiaci VL, Randall M, et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma [abstract]. J Clin Oncol. 2017;35(15 suppl):5505.
28. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2004;22:2159–66.
29. Aghajanian C, Fillaci V, Dizon DS, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol. 2018;150:274–81.
30. Hogberg T, Signorelli M, de Oliveria CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. Eur J Cancer. 2010;46:2422–31.

18 Endometrial Cancer with High-Risk Histology

Seema Singhal

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].

S. Singhal (✉)
Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_18

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].

References

1. National Comprehensive Cancer Network. NCCN guidelines: uterine neoplasms 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473. Accessed 12 Dec 2022.
2. Lu KH, Broaddus RR. Endometrial cancer. N Engl J Med. 2020;383(21):2053–64.
3. Bogani G, Ray-Coquard I, Concin N, Ngoi NY, Morice P, Enomoto T, et al. Uterine serous carcinoma. Gynecol Oncol. 2021;162(1):226–34.
4. Ferriss JS, Erickson BK, Shih IM, Fader AN. Uterine serous carcinoma: key advances and novel treatment approaches. Int J Gynecol Cancer. 2021;31(8):1165–74.
5. WHO Classification of Tumours Editorial Board. World Health Organization classification of tumours. Female genital tumours, 5th ed. Lyon: IARC Press; 2020.
6. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann J, Bosse T, Chargari C, Fagotti A, Fotopoulou C. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12–39.
7. Kumar S, Podratz KC, Bakkum-Gamez JN, Dowdy SC, Weaver AL, McGree ME, et al. Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrial cancer. Gynecol Oncol. 2014;132(1):38–43.
8. Nelson G, Randall M, Sutton G, Moore D, Hurteau J, Look K. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. Gynecol Oncol. 1999;75(2):211–4.
9. Onda T, Yoshikawa H, Mizutani K, Mishima M, Yokota H, Nagano H, et al. Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. Br J Cancer. 1997;75(12):1836–41.
10. Watari H, Katayama H, Shibata T, Ushijima K, Satoh T, Onda T, et al. Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan clinical oncology group study 1412 (SEPAL-P3). Japanese. J Clin Oncol. 2017;47(10):986–90.
11. Persson J, Salehi S, Bollino M, Lönnerfors C, Falconer H, Geppert B. Pelvic sentinel lymph node detection in high-risk endometrial cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging. Eur J Cancer. 2019;116:77–85.
12. Cusimano MC, Vicus D, Pulman K, Maganti M, Bernardini MQ, Bouchard-Fortier G, et al. Assessment of sentinel lymph node biopsy vs lymphadenectomy for intermediate-and high-grade endometrial cancer staging. JAMA Surg. 2021;156(2):157–64.

13. Cusimano MC, Vicus D, Pulman K, Bernardini MQ, Laframboise S, May T, et al. Sentinel lymph node biopsy versus lymphadenectomy for high-grade endometrial cancer staging (SENTOR trial): a prospective multicenter cohort study. Gynecol Oncol. 2020;159:2. https://doi.org/10.1016/j.ygyno.2020.06.003.
14. Capozzi VA, Sozzi G, Monfardini L, Di Donna MC, Giallombardo V, Balbo GL, et al. Transperitoneal versus extraperitoneal laparoscopic aortic lymph nodal staging for locally advanced cervical cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2021;47(9):2256–64.
15. Díaz-Feijoo B, Bebia V, Hernández A, Gilabert-Estalles J, Franco-Camps S, de la Torre J, et al. Surgical complications comparing extraperitoneal vs transperitoneal laparoscopic aortic staging in early stage ovarian and endometrial cancer. Gynecol Oncol. 2021;160(1):83–90.
16. Bebia V, Gil-Moreno A, Hernández A, Gilabert-Estellés J, Franco-Camps S, de la Torre J, et al. Robot-assisted extraperitoneal para-aortic lymphadenectomy is associated with fewer surgical complications: a post hoc analysis of the STELLA-2 randomized trial. J Minim Invasive Gynecol. 2021;28(12):2004–12.
17. Kaban A, Topuz S, Erdem B, Sozen H, Numanoğlu C, Salihoğlu Y. Is omentectomy necessary for non-endometrioid endometrial cancer. Gynecol Obstet Investig. 2018;83(5):482–6.
18. Zhang L, Kwan SY, Wong KK, Soliman PT, Lu KH, Mok SC. Pathogenesis and clinical management of uterine serous carcinoma. Cancers. 2020;12(3):686–91.
19. Xu H, Cui SS, Ran L, Liu Y, Hu C, Xu Y, Tian Y. Incidence of omental metastasis in uterine serous carcinoma: a systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2022;51(6):102395.
20. Chen M, Guo P, Tan J, Liu D, Yao S. The role of omentectomy in the surgical treatment of uterine serous carcinoma. Eur J Obstet Gynecol Reprod Biol X. 2019;4:100084.
21. Chi D, Berchuck A, Dizon DS, Yashar CM. Principles and practice of gynecologic oncology. Philadelphia: Lippincott Williams & Wilkins; 2017.
22. Xu Y, Shen J, Zhang Q, He Y, Chen C, Tian Y. Oncologic safety of laparoscopic surgery for women with apparent early-stage uterine serous carcinoma: a multi-institutional retrospective cohort study. Int J Gynecol Obstet. 2022;158(1):162–71.
23. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022;399(10333):1412–28.
24. Papachristofilou A, Finazzi T. Combination of brachytherapy and chemotherapy not superior to pelvic radiotherapy according to GOG-249. Strahlenther Onkol. 2019;195(6):566–7.
25. Zakem SJ, Robin TP, Smith DE, Amini A, Stokes WA, Lefkowits C, Fisher CM. Evolving trends in the management of high-intermediate risk endometrial cancer in the United States. Gynecol Oncol. 2019;152(3):522–7.
26. Donkers H, Reijnen C, Galaal K, Lombaers MS, Snijders M, Kraayenbrink AA, et al. Defining the optimal treatment strategy in patients with uterine serous carcinoma. Clin Oncol. 2022;35(2):e199–5.
27. Yadav G, Roque DM, Bellone S, Manavella DD, Hartwich TM, Zipponi M, et al. Synergistic activity of neratinib in combination with olaparib in uterine serous carcinoma overexpressing HER2/neu. Gynecol Oncol. 2022;166(2):351–7.
28. Jamieson A, Bosse T, McAlpine JN. The emerging role of molecular pathology in directing the systemic treatment of endometrial cancer. Ther Adv Med Oncol. 2021;13:17588359211035959. https://doi.org/10.1177/17588359211035959.

19 Incompletely Operated Malignant Uterine Neoplasms

Vinotha Thomas

Introduction

Unanticipated discovery of malignant uterine neoplasm following hysterectomy and myomectomy for presumed benign conditions are often referred to gynaecological oncologists for further management. In countries which have national surgical quality programs, heightened concern was expressed for an incidence rate of 1.24% [1] for unexpected uterine malignancies following uterine surgeries. However, this rate could be even higher in developing countries [2]. Majority of these unexpected diagnoses can be secondary to inadequate preoperative clinical evaluation of patients with frank malignancies or uterine surgeries for presumed benign conditions such as fibroids.

Incompletely operated malignant uterine neoplasm poses a risk of inadequate staging of the cancer and also a risk of undertreatment. Sub optimally treated cancers are associated with higher risk of recurrence.A uterus contained malignant neoplasm might be upstaged by inadvertent, incorrect primary surgery. Subsequent restaging of such cases might result in increased postoperative morbidity and delay in adjuvant treatment. The following cases have been discussed to bridge the knowledge gap in management of such clinical predicaments.

Case 1

Age, Parity, PS	60 years P4L4; ECOG = 1
Presenting complaints	Prolapse uterus (third degree cervical descent with second degree cystocele) with 6 months history of postmenopausal bleeding per vaginum
Co-morbidities	Hypertension
Transvaginal sonography	Uterus 7 × 5 × 4 cm, endometrial thickness: Irregular 5 mm, minimal fluid in the canal, bilateral adnexa normal
Surgery	Vaginal hysterectomy with site specific cystocele repair
Histology	Grade 2 endometrioid carcinoma, 1 × 2 cm growth near right cornu >50% MI Extensive LVSI T1bNxMx

Q 1: When Should the Endometrium Be Assessed Prior to Surgery in a Post-menopausal Patient?

Traditionally all postmenopausal women undergoing a hysterectomy for prolapse or other benign conditions were recommended an endometrial

V. Thomas (✉)
Department of Gynaecologic Oncology, Christian Medical College, Vellore, Tamil Nadu, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_19

biopsy to exclude asymptomatic endometrial cancer. Usually in postmenopausal women, the endometrium is atrophic and no curettings are usually obtained and so this practice gradually discontinued for asymptomatic women. Preoperative evaluation of endometrium and pelvic organs is desirable prior to undertaking hysterectomy in these situations. A Pap smear or in countries with no established cervical screening program, evaluation of cervix with VIA (visual inspection with acetic acid) or colposcopy may be advisable. However colposcopy is usually unsatisfactory in this age group because of frequent finding of Type 3 transformation zone in postmenopausal age group.

It is mandatory to perform endometrial evaluation using endometrial aspiration or endometrial biopsies in women presenting with postmenopausal bleeding and or irregular, thickened endometrial lining ≥5 mm [3].However, benign endometrial biopsy in a post-menopausal lady with recently detected large uterine "fibroid "should be interpreted with caution as the sensitivity of endometrial biopsy in detecting uterine sarcoma is low [4]. Uterine sarcomas should be considered as differential diagnosis in recent onset enlargement of uterus in a postmenopausal woman after excluding endometrial carcinoma.

In this case, although post-menopausal bleeding would have been attributed to a hypertrophied cervix secondary to vascular congestion following long standing prolapse, endometrial evaluation prior to surgery based on symptoms and ultrasound findings would have revealed endometrial cancer and prompted timely referral to gynaecological oncologists.

Q: Is Oophorectomy Imperative Along with Hysterectomy in Endometrial Cancer?

Standard surgery in endometrial cancer entails removal of adnexa along with hysterectomy in endometrial cancer to detect its occult, microscopic involvement, reduce risk of recurrence due to continued estrogen production and risk of metachronous ovarian malignancy. In early ovarian cancer, preservation of ovaries does not impact survival [5] and can be considered in young patients who are not at risk for Lynch Syndrome [6]. However, the risk of ovarian involvement increases with high grade histologies, poor differentiation of endometrial cancer, deep myometrial invasion and presence of lymphovascular space invasion [7]. Prophylactic salpingectomy with ovarian conservation can be considered in premenopausal women with low grade, low risk endometrial cancer in the absence of deep myometrial invasion, lymphovascular space invasion or extrauterine disease but needs to be removed in older women or those with high risk disease [8].

Q: How Should this Case Be Managed Further?

As with all referrals, the patient's clinical history, operative details and pathology report need to be reviewed to confirm the diagnosis, for prognostication and further management. The surgical specimen needs to be re-evaluated by a gynaecological onco-pathologist. Factors which increase risk of pelvic and distant metastasis such as coring, bisection or morcellation of the uterus and possible tumour contamination of the vagina or peritoneal cavity by the primary surgery will be revealed by review of operative details and description of the gross specimen by the initial pathology report. Reassessment of the surgical specimen by an experienced gynaecological oncologic pathologist will identify other prognostic factors such as histologic type, grade, depth of myometrial invasion, cervical stromal involvement and presence of lymphovascular space invasion. A CT (computed tomography) scan of the abdomen and pelvis (thorax can be included in case of high-risk histology) with contrast can identify enlarged lymph nodes or peritoneal disease following incomplete surgery. However, post-operative inflammatory changes need to be differentiated from metastatic disease.

Following appropriate clinical evaluation and review, further management needs to be individualized and is dependent upon the identification of histological risk factors and type

of surgery performed. Surveillance may be an option in the absence of uterine morcellation/bisection or resection in small tumours, low grade histology and superficial myometrial invasion, following hysterectomy and bilateral salpingo-oopherectomy [9]. In patients at intermediate to high risk of recurrence, or in the presence of intrabdominal extrauterine disease, in a surgically fit patient, comprehensive restaging following tailored adjuvant treatment or adjuvant treatment alone can be discussed.

In the above clinical scenario, in view of deep myometrial invasion and extensive LVSI in the surgical specimen, with conservation of adnexae, comprehensive restaging with pelvic and para-aortic lymphadenectomy will allow excision of any microscopic disease, assign an appropriate FIGO (International Federation of Gynecology and Obstetrics) stage and allow removal of adnexae to exclude microscopic disease involvement and eliminate potential source of estrogen. If the patient is unfit or declines surgery, pelvic radiation can be offered in view of deep myometrial involvement and extensive lymphovascular space invasion. In case of obvious extrauterine disease on radiological imaging, both upfront restaging or neoadjuvant chemotherapy followed by restaging can be considered as per patient's fitness for surgery, after discussion with the patient. In the presence of obvious disease spread, complete tumour cytoreduction with removal of enlarged lymph nodes should be considered if macroscopic complete cytoreduction is possible with acceptable morbidity [10].

Q: Discuss the Prognosis of the Case

Case 1

She underwent bilateral salpingoophorectomy with, bilateral pelvic and para-aortic lymphadenectomy in view of extensive LVSI.

HPE: adnexa and lymph nodes free of tumor.

Stage I B with substantial LVSI would place the patient at high to intermediate risk of recurrence. Combination of clinicopathological factors with molecular risk profile will improve prognostication. In immunohistochemistry, if the tumour shows abnormal p53 expression, the patient is at high risk of recurrence and therefore comprehensive staging is recommended.

Q: Further Management?

In view of deep myometrial invasion and lymph vascular space invasion, she is at high intermediate risk of recurrence. Adjuvant pelvic radiation (external beam) will decrease the 2 year cumulative recurrence risk from 27% to 13% [11]. Radiation should be initiated within 6–8 week from date of surgery.

Molecular risk profiling allows objective prognostication of endometrial cancer. If the tumour shows abnormal p53 expression, addition of chemotherapy to radiation can be discussed and considered to reduce the high risk of recurrence [12].

Case 2

Age, Parity, PS	48 years, P3L3 previous 3 LSCS, ECOG = 1
History	Heavy menstrual bleeding with clots, uterus −18 weeks size, hemoglobin 4gm% Emergency ultrasound: Fibroid uterus (submucous) Not responding to conservative management
Surgery	Emergency subtotal abdominal hysterectomy
Histology	Grade 1 endometrioid carcinoma, 2 × 3 cm in the anterior wall>50% MI Substantial LVSI+ Leiomyoma uterus anterior and fundal location 6 cm

Q: Options for Further Management?

Management of inappropriately managed endometrial cancer is individualized based on details of the primary surgery, the risk of the patient har-

bouring residual or metastatic disease and the risk of recurrence. In the above-described case, as the histopathology report shows deep myometrial invasion and lymphovascular space invasion, the patient is at a high risk of both residual and metastatic disease. In this patient, who is younger than the median age of endometrial cancer, detailed family history should also be elicited, besides immunohistochemical testing of tumour tissue for mismatch repair (MMR) proteins and p53. After clinical examination, advanced radiological imaging such as CT scan of abdomen or pelvis or MRI (magnetic resonance imaging) abdomen and pelvis will help exclude obvious metastatic or residual disease.

In the absence of obvious macroscopic residual or metastatic disease, comprehensive surgical staging which includes removal of cervical stump, adnexae, pelvic and para-aortic lymphadenectomy should be offered to this patient. Though prospective trials have not shown therapeutic benefit of lymphadenectomy, it helps to prognosticate and tailor adjuvant therapy [13, 14]. As mentioned above, in the presence of gross residual disease or metastatic disease, decision to offer upfront debulking surgery or after neoadjuvant chemotherapy should be discussed and developed subject to surgical efforts to obtain complete cytoreduction and patient's performance status.

Patient underwent cervical stump excision+ bilateral pelvic and para-aortic lymphadenectomy
Histology: Cervical stromal involved by Grade 1 endometrioid cancer. Parametrial and lymph nodes: uninvolved

Q: Further Management?

In view of deep myometrial invasion and substantial lymphovascular space involvement, adjuvant external beam radiation (EBRT) to the pelvis should be offered to the patient. In view of cervical stromal involvement, EBRT should be followed by vaginal brachytherapy. Adjuvant chemotherapy can be added to radiation in case of immunohistochemical demonstration of p53 abnormality. Besides its other advantages, testing for MMR deficiency using IHC will help triage for genetic testing to identify patients with Lynch Syndrome [15]. Molecular profiling using POLE testing may also be beneficial if available.

Case 3

Age, Parity, PS	17-year-old schoolgirl, single
History	Heavy menstrual bleeding with anemia, uterus −16 weeks size MRI scan: Submucous fibroid
Surgery	Laparoscopic myomectomy with in bag morcellation
Histology	Endometrial stromal tumour, consistent with low grade endometrial stromal sarcoma, morcellated myomectomy specimen Lymphovascular space invasion, present

Q: What Is the Role of MRI in Identification of Endometrial Stromal Sarcomas?

Endometrial stromal sarcomas, unlike the other uterine sarcomas, often affects younger women between 40–55 years of age [16]. Though an indolent tumour, it is characterized by extrauterine disease, late metastasis and recurrence. As it is a rare tumour, with a non-specific presentation, it is often misdiagnosed as a benign leiomyoma or adenomyosis in young women.

Pretreatment identification of uterine sarcomas by MRI has been a challenge. Though diffusion weighted MRI has been highlighted as a potential tool in identification of leiomyosarcoma, there is paucity of evidence supporting its role of LGESS (low grade endometrial stromal sarcoma. Characteristic MRI features reported in low grade ESS include: worm like nodular extension, intra tumoural low signal intensity (SI) bands, cystic or necrotic change, absence of speckled appearance on T2 weighted images and low apparent diffusion coefficient value.

However, these findings need to be validated, out of trial setting [17].

In this case, unanticipated differential diagnosis of LGESS in a 17 year old, non-specific symptoms and overlap of radiological findings with leiomyoma would have led to a misdiagnosis of LGESS, though MRI is often the only reliable tool available in preoperative diagnosis in these patients. On the contrary, a preoperative diagnosis of endometrial stromal sarcoma would have been a clinical dilemma in a 17-year-old.

Q: What Are the Further Management Options? Surveillance Vs Completion Surgery—Critically Evaluate

A histopathological review of the surgical specimen is mandatory to exclude differential diagnoses such as leiomyoma, endometrial stromal nodule and high grade /undifferentiated endometrial stromal sarcoma. LGESS is differentiated from endometrial stromal nodules by the presence of myometrial and lymphovascular space invasion. Besides microscopic appearance, immunoreactivity to CD 10, cyclin D1, estrogen and progesterone receptors and cytogenic abnormality demonstrated by fluorescence in situ hybridization or reverse transcriptase–polymerase chain reaction will help differentiate LGESS from high grade ESS and undifferentiated sarcomas. MRI pelvis will help assess for residual disease. CT scan of abdomen and thorax will exclude metastatic disease.

Even in the absence of residual or metastatic disease, uterus preserving surgery is not the standard of care for LGESS. However, in a select group of reported cases, and case series, uterus preserving surgery has resulted in pregnancies [18, 19]. There is a lack of guidelines for selection of patients for uterus preservation and these patients are at risk for both local recurrence and distant metastasis [20, 21].

Hysterectomy is the standard of care in low grade ESS. Preservation of ovaries may be associated with higher recurrence rate but might be considered in very young patients with uterus confined disease as these recurrences are usually salvageable [22]. However, the parents and the patient in particular, might not accept hysterectomy in view of her age and hence need to be counselled adequately about its safety, hazards, feasibility and the need for adequate surveillance in view of high risk of recurrence.

The patient refused hysterectomy and was lost to follow up subsequent to the onset of COVID pandemic. She reported 2 years later with abnormal menstrual bleeding and 16 weeks size uterus. CT scan of the thorax, abdomen and pelvis (Fig. 19.1a, b) showed recurrent uterine tumour, right iliac fossa port side metastasis, left external iliac nodal enlargement, left moderate hydroureteronephrosis and infrarenal inferior vena caval (IVC) thrombus.

Q: Discuss Management with Regard to the Current Scenario

Low grade endometrial stromal sarcoma, though an indolent tumour, is characterized by hematogenous spread, venous thrombosis and recurrence in about one-third [23]. These indolent tumours are not chemo sensitive. Surgery is the mainstay of treatment even in advanced metastatic disease and the tumour should be completely cytoreduced if feasible [24].

Prior to surgery, this patient needs an IVC filter to prevent pulmonary thromboembolism as uterine bleeding might worsen with anticoagulation. She needs correction of anemia, nutritional rehabilitation. Most importantly she will need to consent for hysterectomy, oophorectomy, metastatectomy, including removal of venous thrombus [25]. The consent should also include possible intraoperative and post-operative complications, chances of suboptimal cytoreduction, need for adjuvant treatment, post-surgery surveillance and likelihood of recurrence in view of metastatic disease [26].

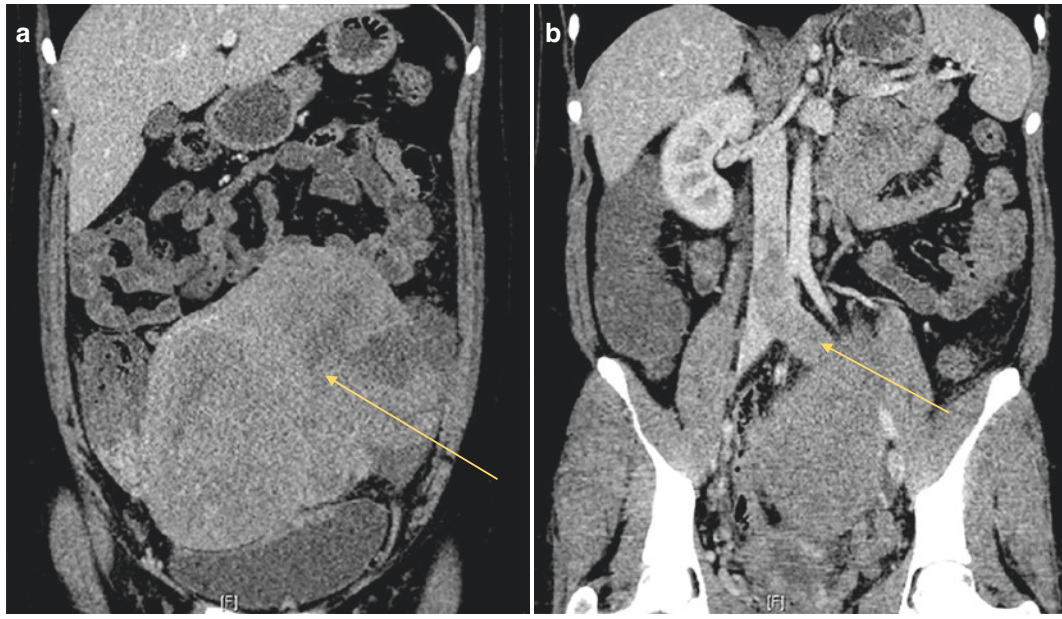


Fig. 19.1 (**a**) Coronal view of CT abdomen and pelvis with contrast with the arrowhead showing recurrent uterine tumour. (**b**) A coronal view with arrowhead showing the IVC thrombus

The patient underwent cytoreductive surgery - abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy, left parametrectomy, left ureterolysis, enlarged left pelvic lymph node removal, port site and IVC thrombus metastatectomy. The histopathology was reported as: low grade ESS with ovarian,parametrial, omental and port site and IVC thrombus involvement

Q: What Would Be the Adjuvant Treatment Advised?

Almost all cases of LGESS express estrogen and progesterone receptors. In steroid receptor positive tumours, in advanced or recurrent disease, hormonal therapy is the standard of care after surgery or in inoperable cases and has been found to improve long term survival [27]. Both partial and complete responses have been reported. Hormonal therapy includes options such as progestins, aromatase inhibitors along with bisphosphonates and gonadotropin-releasing hormone analogues [28]. Tamoxifen is however contraindicated. Patients need to be counselled with regard to periodic surveillance with clinical and radiological examination.

There is no recommendation with regard to duration of therapy and hormonal therapy is recommended as long as tolerated, in the absence of recurrence [28].Palliative chemotherapy or radiation can be offered in the non-responders to hormone therapy.

Case 4

Age, Parity, PS	35 years, P2L2, ECOG = 1
History	Lump abdomen and increased frequency of micturition × 6 months No menstrual complaints Uterus enlarged to 16–18 weeks size
Imaging	10 cm multiloculated cystic expansile lesion in fundal and anterior myometrium displacing endometrial canal posteriorly. Irregular solid component in periphery. Bilateral adnexa normal Impression: Leiomyoma with cystic degeneration
Surgery	Abdominal hysterectomy with bilateral salpingectomy
Histology	Leiomyosarcoma

Q: Discuss the Possibility of Preoperative Diagnosis of Leiomyosarcoma

Preoperative diagnosis of leiomyosarcomas is challenging as symptoms such as abdominal mass, pelvic pain, pressure and bleeding are encountered in both leiomyomas and leiomyosarcomas. However malignant tumour should be considered in a fibroid-like setting in menopausal women as leiomyosarcomas have a preponderance in women above 50 years of age [29].

Ultrasound scan is often the mainstay of diagnosis of leiomyomas which are sonographically characterized as well defined, solid, hypoechoic tumors with calcification. However atypical benign lesions might show heterogeneous echogenicity and central necrosis, similar to leiomyosarcomas and are difficult to differentiate. Large sized tumours, cystic degeneration with increased vascularity on colour doppler ultrasound might suggest leiomyosarcomas, but these findings have low accuracy [30]. In premenopausal women, when there is a clinical suspicion of leiomyosarcoma, based on clinical findings, recent enlargement of uterus or non-classical ultrasound findings of a presumed fibroid, MRI with contrast may be a more reliable tool than ultrasound in diagnosis. Typical MRI features include nodular borders and irregular contours, intralesional hemorrhage and necrosis, T2 dark areas, and central unenhanced areas. As other benign mesenchymal variants might share overlapping features with leiomyosarcomas, combination of the above mentioned characteristics might improve the accuracy of MRI in preoperative diagnosis of leiomyosarcoma [31].Combining MRI scan with preoperative evaluation of LDH can be useful in differentiating leiomyosarcoma from leiomyoma [32]. In view of predominant myometrial involvement, a negative endometrial biopsy should be interpreted with caution in clinically suspected leiomyosaroma.

Hence women of older age group or postmenopausal women with recent onset uterine enlargement, in the absence of classical radiological findings of fibroid, should be suspected to have uterine leiomyosarcoma and should be considered for en bloc total hysterectomy.

Q: What Would Be the Further Management?

Following referral to a gynecologic oncologist, the surgical notes need to be reviewed to exclude peritoneal spill of tumour. The surgical slides and blocks have to be subjected to pathology review to exclude leiomyoma variants, smooth muscle tumours of undetermined malignant potential (STUMP), other uterine sarcomas and endometroid carcinoma. A CT scan of the thorax, abdomen and pelvic or a PET (positron emission tomography) CT will help identify residual disease or metastatic disease.

In the above clinical scenario described, if the patient has undergone en bloc hysterectomy and salpingectomy, repeat surgery is not required to remove the ovaries [33]. However, following a myomectomy or morcellation, re-exploration of the abdomen followed by hysterectomy and excision of peritoneal deposits is recommended [34].

Q: Discuss Further Management

Leiomyosarcomas are aggressive tumours and tend to metastasize, even in early disease. However, neither radiation [35] nor chemotherapy [36, 37] has been found to improve overall survival in early stage optimally resected tumours. Adjuvant treatment can be reserved for advanced disease.

Conclusion

Surgery is the mainstay of treatment of malignant uterine neoplasms such as endometrial carcinomas or uterine sarcomas. However, following inadvertent surgery, the role of comprehensive surgical restaging of the patient needs to be individualized and balanced as per

the clinical condition, the need for complete cytoreduction, prognostication and FIGO stage assignment and subsequent tailoring of adjuvant therapy versus the morbidity of repeat surgery and delay in adjuvant treatment.

Key Points

Following referral of an incompletely stage malignant uterine neoplasm, it would be prudent to

1. Review the surgical notes and histopathological specimen
2. Assess risk of residual disease and metastatic disease with advanced radiological imaging
3. Based on histopathological review and radiological findings, discuss prognosis and need for adjuvant treatment in a multidisciplinary forum
4. Consider surgical restaging to excise residual disease or metastatic disease or to assign stage and tailor adjuvant therapy
5. Avoid delay of adjuvant therapy due to surgical restaging or in cases at low risk of recurrence if hysterectomy has been completed

References

1. Mahnert N, Morgan D, Campbell D, Johnston C, As-Sanie S. Unexpected gynecologic malignancy diagnosed after hysterectomy performed for benign indications. Obstet Gynecol. 2015;125(2):397–405. https://doi.org/10.1097/AOG.0000000000000642.
2. Yadav G, Rao M, Goyal SB, Singh P, Kathuria P, Gothwal M. Risk of incidental genital tract malignancies at the time of myomectomy and hysterectomy for benign conditions. Obstet Gynecol Sci. 2021;64(2):209–15. https://doi.org/10.5468/ogs.20199.
3. ACOG Committee Opinion No. 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018;131(5):e124–9. https://doi.org/10.1097/AOG.0000000000002631.
4. Hinchcliff EM, Esselen KM, Watkins JC, Oduyebo T, Rauh-Hain JA, Del Carmen MG, Quade BJ, Muto MG. The role of endometrial biopsy in the preoperative detection of uterine Leiomyosarcoma. J Minim Invasive Gynecol. 2016;23(4):567–72. https://doi.org/10.1016/j.jmig.2016.01.022.
5. Shin W, Park SY, Kang S, Lim MC, Seo SS. The survival effect of ovary preservation in early stage endometrial cancer: a single institution retrospective analysis. J Ovarian Res. 2020;13(1):97. https://doi.org/10.1186/s13048-020-00698-5.
6. Matsuo K, Machida H, Shoupe D, Melamed A, Muderspach LI, Roman LD, Wright JD. Ovarian conservation and overall survival in young women with early-stage low-grade endometrial cancer. Obstet Gynecol. 2016;128(4):761–70. https://doi.org/10.1097/AOG.0000000000001647.
7. Ignatov T, Eggemann H, Burger E, Ortmann O, Costa SD, Ignatov A. Ovarian metastasis in patients with endometrial cancer: risk factors and impact on survival. J Cancer Res Clin Oncol. 2018;144(6):1103–7. https://doi.org/10.1007/s00432-018-2628-2.
8. Hamilton CA, Pothuri B, Arend RC, Backes FJ, Gehrig PA, Soliman PT, et al. Endometrial cancer: a society of gynecologic oncology evidence-based review and recommendations, part II. Gynecol Oncol. 2021;160(3):827–34. https://doi.org/10.1016/j.ygyno.2020.12.024.
9. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, Podratz KC. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008;109(1):11–8. https://doi.org/10.1016/j.ygyno.2008.01.023.
10. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12–39. https://doi.org/10.1136/ijgc-2020-002230.
11. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. Gynecologic oncology group. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a gynecologic oncology group study. Gynecol Oncol. 2004;92(3):744–51. https://doi.org/10.1016/j.ygyno.2003.11.048.
12. León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. TransPORTEC consortium. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol. 2020;38(29):3388–97. https://doi.org/10.1200/JCO.20.00549.
13. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125–36. https://doi.org/10.1016/S0140-6736(08)61766-3.
14. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707–16. https://doi.org/10.1093/jnci/djn397.

15. Cho KR, Cooper K, Croce S, Djordevic B, Herrington S, Howitt B, et al. International Society of Gynecological Pathologists (ISGyP) Endometrial Cancer Project: guidelines from the Special Techniques and Ancillary Studies Group. Int J Gynecol Pathol. 2019;38 Suppl 1(Iss 1 Suppl 1):S114–22. https://doi.org/10.1097/PGP.0000000000000496.
16. Mbatani N, Olawaiye AB, Prat J. Uterine sarcomas. Int J Gynaecol Obstet. 2018;143(Suppl 2):51–8. https://doi.org/10.1002/ijgo.12613.
17. Himoto Y, Kido A, Sakata A, Moribata Y, Kurata Y, Suzuki A, et al. Differentiation of uterine low-grade endometrial stromal sarcoma from rare leiomyoma variants by magnetic resonance imaging. Sci Rep. 2021;11(1):19124. https://doi.org/10.1038/s41598-021-98473-z.
18. Laurelli G, Falcone F, Scaffa C, Messalli EM, Del Giudice M, Losito S, Greggi S. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:61–6. https://doi.org/10.1016/j.ejogrb.2015.09.041.
19. Xie W, Cao D, Yang J, Jiang X, Shen K, Pan L, Huang H, et al. Fertility-sparing surgery for patients with low-grade endometrial stromal sarcoma. Oncotarget. 2017;8(6):10602–8. https://doi.org/10.18632/oncotarget.12491.
20. Dondi G, Porcu E, De Palma A, Damiano G, De Crescenzo E, Cipriani L, et al. Uterine preservation treatments in sarcomas: oncological problems and reproductive results: a systematic review. Cancers (Basel). 2021;13(22):5808. https://doi.org/10.3390/cancers13225808.
21. Zheng Y, Yin Q, Yang X, Dong R. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series, a population-based analysis and review of the literature. Ann Transl Med. 2020;8(21):1358. https://doi.org/10.21037/atm-20-2180.
22. Nasioudis D, Ko EM, Kolovos G, Vagios S, Kalliouris D, Giuntoli RL. Ovarian preservation for low-grade endometrial stromal sarcoma: a systematic review of the literature and meta-analysis. Int J Gynecol Cancer. 2019;29(1):126–32. https://doi.org/10.1136/ijgc-2018-000063.
23. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol. 1990;14(5):415–38. https://doi.org/10.1097/00000478-199005000-00002.
24. Capozzi VA, Monfardini L, Ceni V, Cianciolo A, Butera D, Gaiano M, Berretta R. Endometrial stromal sarcoma: a review of rare mesenchymal uterine neoplasm. J Obstet Gynaecol Res. 2020;46(11):2221–36. https://doi.org/10.1111/jog.14436.
25. Renzulli P, Weimann R, Barras JP, Carrel TP, Candinas D. Low-grade endometrial stromal sarcoma with inferior vena cava tumor thrombus and intracardiac extension: radical resection may improve recurrence free survival. Surg Oncol. 2009;18(1):57–64. https://doi.org/10.1016/j.suronc.2008.07.003.
26. Zhang Y, Li Y, Huang H, Yang J, Wu M, Jin Y, Pan L. Low-grade endometrial stromal sarcoma and uterine adenosarcoma: a comparison of clinical manifestations and outcomes. J Cancer. 2019;10(15):3352–60. https://doi.org/10.7150/jca.30691.
27. Ferrandina G, Aristei C, Biondetti PR, Cananzi FCM, Casali P, Ciccarone F, et al. Italian consensus conference on management of uterine sarcomas on behalf of S.I.G.O. (Societa' italiana di Ginecologia E Ostetricia). Eur J Cancer. 2020;139:149–68. https://doi.org/10.1016/j.ejca.2020.08.016.
28. Reich O, Regauer S. Hormonal therapy of endometrial stromal sarcoma. Curr Opin Oncol. 2007;19(4):347–52. https://doi.org/10.1097/CCO.0b013e3281a7ef3a.
29. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, Yordan E, Brady MF. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71(4 Suppl):1702–9. https://doi.org/10.1002/cncr.2820710440.
30. Sun S, Bonaffini PA, Nougaret S, Fournier L, Dohan A, Chong J, et al. How to differentiate uterine leiomyosarcoma from leiomyoma with imaging. Diagn Interv Imaging. 2019;100(10):619–34. https://doi.org/10.1016/j.diii.2019.07.007.
31. Lakhman Y, Veeraraghavan H, Chaim J, Feier D, Goldman DA, Moskowitz CS, Nougaret S, Sosa RE, Vargas HA, Soslow RA, Abu-Rustum NR, Hricak H, Sala E. Differentiation of uterine leiomyosarcoma from atypical leiomyoma: diagnostic accuracy of qualitative MR imaging features and feasibility of texture analysis. Eur Radiol. 2017;27(7):2903–15. https://doi.org/10.1007/s00330-016-4623-9.
32. Goto A, Takeuchi S, Sugimura K, Maruo T. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer. 2002;12(4):354–61. https://doi.org/10.1046/j.1525-1438.2002.01086.
33. Nasioudis D, Chapman-Davis E, Frey M, Holcomb K. Safety of ovarian preservation in premenopausal women with stage I uterine sarcoma. J Gynecol Oncol. 2017;28(4):e46. https://doi.org/10.3802/jgo.2017.28.e46.
34. Oduyebo T, Rauh-Hain AJ, Meserve EE, Seidman MA, Hinchcliff E, George S, et al. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014;132(2):360–5. https://doi.org/10.1016/j.ygyno.2013.11.024.
35. Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol

55874). Eur J Cancer. 2008;44(6):808–18. https://doi.org/10.1016/j.ejca.2008.01.019.

36. Rizzo A, Nannini M, Astolfi A, Indio V, De Iaco P, Perrone AM, et al. Impact of chemotherapy in the adjuvant setting of early stage uterine leiomyosarcoma: a systematic review and updated meta-analysis. Cancers (Basel). 2020;12(7):1899. https://doi.org/10.3390/cancers12071899.
37. Bogani G, Fucà G, Maltese G, Ditto A, Martinelli F, Signorelli M, et al. Efficacy of adjuvant chemotherapy in early stage uterine leiomyosarcoma: a systematic review and meta-analysis. Gynecol Oncol. 2016;143(2):443–7. https://doi.org/10.1016/j.ygyno.2016.07.110.

Recurrent Endometrial Cancer

20

Kavita Singh and Bindiya Gupta

Introduction

Management of recurrent endometrial cancer has undergone modifications in recent times following the molecular profiling of endometrial cancers. Rate of recurrences is 7–15% of stage1/II endometrial cancers [1–3]. Recurrences are more common with type 2 cancers, higher stages and those with associated risk factors like older age and lymphovascular space invasion. Risk stratification has been further modified with the molecular profiling of endometrial cancers and treatment of recurrent endometrial cancer therefore ranges from hormonal treatment, immunotherapy, chemotherapy+radiotherapy or surgery alone. Careful work up is essential of recurrent endometrial cancer to understand the pattern of recurrence whether it is local on the vaginal vault, regional in pelvic sidewall or other pelvic structures and distant to lungs, liver or any other extrapelvic organs. Majority of recurrences are locoregional (50%), distant recurrences are seen in 25% and rest 25% recurrences are seen with both distant and locoregional [3].

Traditionally, for localized recurrences on the vault the treatment used to be ablative either with radiotherapy in radiotherapy naïve patients or surgical local excision or an exenterative procedure in patients who have received radiotherapy during their primary disease presentation. Type of surgery offered is dependent upon the size of recurrence, location and number of sites of recurrence. Cytoreduction with complete resection is associated with favourable improvement in overall survival and progression free survival. Systemic therapies like hormonal treatments were administered for distant metastasis with estrogen and progesterone receptor positive tumours. Systemic chemotherapy was given for multisite recurrences and especially for type 2 endometrial cancers (serous/clear cell/carcinosarcoma). However management of recurrent endometrial cancer has undergone transformation with molecular profiling of endometrial cancers.

Now all patients of endometrial cancers have their molecular profiling and are tested for MMR, P53 and POLE if they are not identified as low risk. Now based on this, patients who are P53 positive are treated with chemotherapy, MMR deficient are treated with immunotherapy, non specific molecular profile (NSMP) are given hormonal treatment if found to be estrogen receptor (ER) & progesterone receptor (PR) positive. Immunotherapy treatments are expensive and not easily available, therefore surgical excision for pelvic confined disease is still a norm for management of recurrent endometrial cancer if possible for localised pelvic recurrence.

K. Singh (✉)
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_20

Case 1

Age, Parity, PS	60 years, nulliparous ECOG = 1
Presenting complaints	Complained of abdominal distension × 7 days associated with vomiting and pain abdomen Unable to pass stools and flatus × 2 days Previously FIGO stage 1b grade 3 endometrioid adenocarcinoma. IHC: ER + ve, loss of MSH6 Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, laparoscopic bilateral pelvic lymphadenectomy 3 years ago Received adjuvant vaginal brachytherapy
Co morbidities	Hypertension controlled on amlodipine 5 mg OD
Examination	Abdominal distension, guarding + rigidity +
X ray	Dilated ascending and transverse colon with multiple air fluid levels, no gas below diaphragm s/o intestinal obstruction
CECT abdomen and pelvis	Enhancing soft tissue mass lesion 3 cm in the sigmoid colon narrowing the colonic lumen. Mild infiltration of the pericolonic fat. Enlarged left external and internal iliac nodes 1–2 cm No disease in the pelvis or another other site in the abdomen
Surgery	Resection and anastomosis, removal of bulky lymph nodes on the left side
Histology	Metastatic colon cancer, endometrial in origin, PAX8 positive ER & PR positive (Aldred score 8/8), CDX2 negative, metastatic disease in 2/4 pelvic lymph nodes, resection margins of bowel clear of endometrial cancer
Adjuvant treatment	Received hormonal treatment Planned for immunotherapy with PDL1 inhibitors

Q: Decision Making for Management of this Patient

Careful decision making is required regarding the management of recurrent endometrial cancer. All these cases need a careful discussion in a multidisciplinary team meeting. Several factors which may influence the decision regarding further management are previous stage, histology, molecular profile of tumour, performance status, associated medical comorbidities and previous treatments received. The type of treatment proposed will be also dependent upon the site, number and patterns of recurrences.

The above patient maintains a good performance status and had no major medical comorbidities. She presented with unsuspected locoregional recurrence with acute bowel obstruction requiring emergency palliative surgery. Fortunately she was able to have complete cytoreduction for the recurrent disease.

Further adjuvant treatments to consider are radiotherapy, systemic therapies with chemotherapy, immunotherapy, targeted therapies and hormonal therapies.

Radical dose of radiotherapy to pelvis is associated with both gastrointestinal and urinary tract radiation toxicities. One would therefore favour systemic therapy rather than radiotherapy in view of recent bowel resection and anastomosis.

Traditionally the chemotherapy for recurrent metastatic endometrial cancer consists of Doxorubicin with paclitaxel and cisplatin. This regimen TAP was for a long period, the most effective evidence-based therapy with a significantly higher response rate of 57% versus 34% for AP ($P < 0.01$), and improved PFS (median, 8.3 v 5.3 months; $P < 0.01$), and OS (median, 15.3 v 12.3 months; $P = 0.037$). However, toxicity, and especially neurological toxicity, as well as cardiac toxicity, were a major concern in this elderly population, and many centers started to use carboplatin and paclitaxel instead, with similar results. In 2020, the long-awaited randomized non-inferiority study GOG0209 comparing carboplatin and paclitaxel with paclitaxel, doxorubicin, and cisplatin confirmed that carboplatin and paclitaxel is not inferior to TAP [4].

Immunotherapy with checkpoint inhibitors, both PD1 and PDL1 inhibitors is gaining increasing role in treatment of recurrent and advanced stage metastatic endometrial cancer which has progressed following platinum based chemotherapy. Their efficacy is proven more in MMRd (mismatch repair gene-deficient) and MSI-H (microsatellite instability -high) groups. It is therefore crucial to have molecular profiling of all the endometrial cancers. Pembrolizumab and dostarlimab are currently approved by the EMA and/or FDA for treatment of patients with recurrent or advanced deficient mismatch repair (dMMR) endometrial cancer [5]. In

recurrent endometrial cancer patients pembrolizumab and lenvatinib are effective irrespective of MSI/MMR status, with an inferior response rate of 36% for MSS/pMMR compared to a response rate of 64% in MSI-H/MMRD [6]. This combination therapy has been approved by FDA and addressed in the KEYNOTE-775/Study 309, a randomized phase III trial for endometrial cancer patients with tumors that are not deficient mismatch repair or MSI high and who have recurrent disease following prior systemic therapy. For this combination of lenvatinib and pembrolizumab, the median OS improved from 12 months to 17.4 months, with an HR 0.68 (95% CI 0.56–0.84) (Makker, abstract SGO 2021).

Immunotherapy drugs are expensive and have their associated side effects and not accessible in all the countries. Careful selection of cases for immunotherapy is therefore important.

Hormonal therapy has been used for recurrent endometrial cancer and several studies have shown a variable response. Hormonal therapy is more suitable for type 1 endometrial cancer with ER& PR expression. Progestins have been used with a variable response rate from 11% to 56%. The response rate is high with a longer progression free interval.

Tamoxifen and aromatase inhibitors have an inferior response rate and therefor are regarded as second line hormonal therapy. Above patient was highly expressive for ER and PR receptors and therefore progestins like Megace may be prescribed.

Targeted therapies have limited benefit in recurrent endometrial cancer and therefore not recommended.

Systemic therapy in recurrent endometrial cancer is summarized in fig. 20.1.

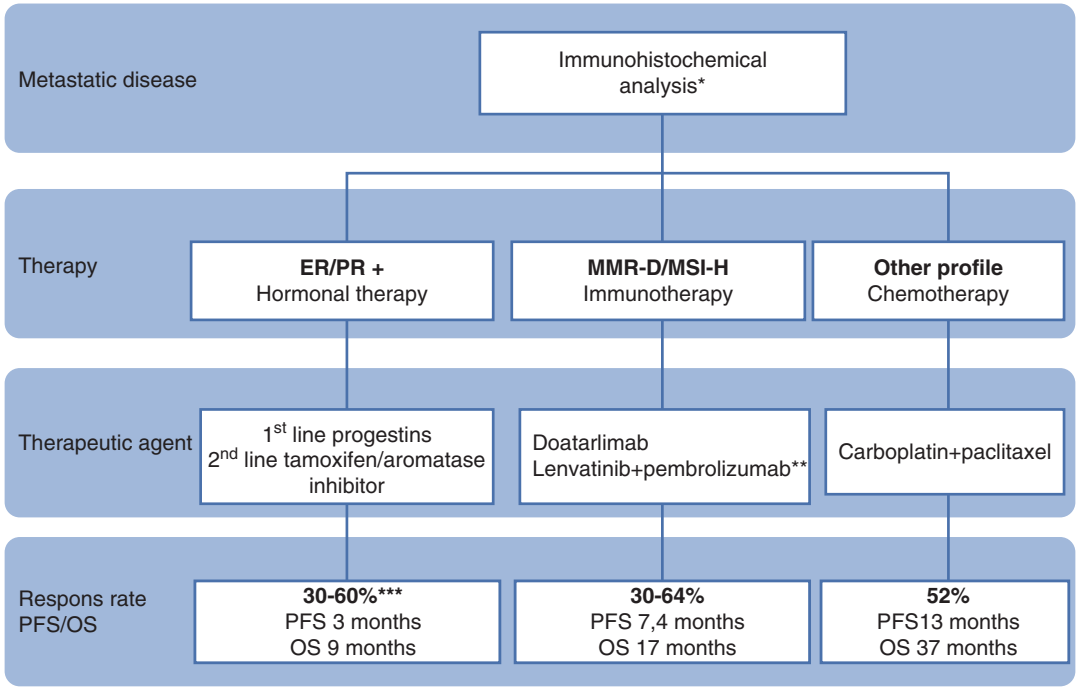


Fig. 20.1 Overview of systemic treatment options in recurrent endometrial cancer. *ER* estrogen receptor, *PR* progesterone receptor, *MMR-D* mismatch repair deficient, *MSI* microsatellite instability, *MSS* microsatellite stable, *pMMR* proficient mismatch repair, *PFS* progression-free survival, *OS* overall survival. * Preferably histology on recurrent tumor ** also approved for pMMR/MSS *** Dependent on level of expression. (Adapted from: Rütten, H.; Verhoef, C.; van Weelden, W.J.; Smits, A.; Dhanis, J.; Ottevanger, N.; Pijnenborg, J.M.A. Recurrent Endometrial Cancer: Local and Systemic Treatment Options. Cancers 2021, 13, 6275. https://doi.org/10.3390/cancers13246275) [7]

Case 2

Age, Parity, PS	65 years, P1 + 0 ECOG = 1
Presenting complaints	Abdominal pain and tenesmus Previous TLH + BSO for stage 1A G1 endometrial cancer 2 years back Now with suspected 6 cm recurrent vaginal vault mass with right hydronephrosis with stent
Co morbidities	Diabetes on metformin controlled
Treatment given	3 cycles chemo carboplatin + paclitaxel (no response) following which was started Provera for 3 months and still had disease progression. Clinically and radiologically the pelvic mass had increased to 8 cm mass involving the right vaginal vault

Q: Discuss Further Investigation, Management and Prognosis of this Case

This case of vaginal vault mass requires a careful work up. It is not very common for a low risk endometrial cancer to recur in 2 years time. It is therefore crucial to review the previous histopathology by onco pathologist to obtain information about the histological findings of the primary treatment – which includes the histological subtypes, molecular profile (MMR status, ER&PR receptor status, POLE and P53), kidney function tests to assess the impact of mass on the hydronephrotic kidney. We may require a DMSA scan to assess the function of hydronephrotic kidney. Histological confirmation is crucial with image guided biopsy to exclude development of a second primary. She requires a PET-CT to assess the distribution of disease/suspected recurrence. An MRI scan is required to assess local extent and tissue planes to determine operability of this tumour and to discuss the type of surgical procedure which will be required.

Grade 1 endometroid tumours do not respond to chemotherapy and may not have been the appropriate management for a suspected recurrent endometrial cancer. Histological confirmation is a must before commencement of chemotherapy. After histological confirmation and if recurrence is proved to be of previously treated Grade 1 endometroid endometrial cancer then molecular profiling and ER PR receptor status assessment is required.

Surgery remains the mainstay of treatment of surgically salvageable localised pelvic recurrences. MRI and clinical examination helps delineate the type and radicality of surgery required. As there is presence of right side unilateral hydronephrosis, involvement of the right side ureter or ureterovesical junction is inevitable.

After carefully evaluating the PETCT, MRI and discussion in the MDT, this patient should have an examination under anaesthesia with cystoscopy and rectosigmoidoscopy.

Further radical surgical excision will be aimed at obtaining complete excision with clear margins which may be just sufficient treatment in absence of evidence of any site of disease. If, however, complete excision of tumour is not obtained and microscopic involvement of margins is present then additional treatment with pelvic radiotherapy may be required which maybe followed by hormone maintenance therapy in patients with ER&PR positive tumours.

Treatment is palliative in cases of incomplete surgical excision of tumour recurrence and this maybe further controlled with pelvic radiotherapy and hormone therapy in patients with ER&PR positive tumours.

Surgery in such large tumour recurrence with possible involvement of bowel and urinary tract is likely to be total pelvic exenteration. Extent of surgery is tailored to the disease distribution and aim is to be conservative for visceral sparing, as long as the oncological principles of obtaining complete resection are not compromised e.g. if bladder and anterior vagina is not involved then bladder maybe spared with excision and reimplantation of the right ureter with Boari flap and psoas hitch. If the recurrent mass involves the right pelvic side wall then more radical endopelvic resection may be required with ligation of internal iliac vessels and removal of obturator internus muscle if involved. Lateral pelvic recurrences which are larger than 6 cm and encroaching greater sciatic

notch or lumbosacral plexus are relative contraindication for extended endopelvic resection.

Long term outcome for patients with complete resection is good with 50–80% survival. However, with involved excision margins the prognosis becomes grim with 10–30% survival.

Case 3

Age, Parity, PS	54 years, P2 + 0 ECOG = 1
Clinical presentation	Recurrent endometrioid endometrial cancer (WT1 negative, CK 7 and PAX-8 positive) after 5 years Presented with abdominal pain and lump abdomen History of synchronous corpus 1A and 1C endometrioid adeno carcinoma of the ovary Treated with surgery and adjuvant chemotherapy
Co morbidities	None
CECT abdomen and pelvis	Right inguinal nodes 11 × 9 mm. Mass in rectus muscle 6 × 4 cm. Pelvic sidewall mass 14 × 12 mm. Subcapsular deposit 2 cm on the liver, kidneys, pancreas or spleen normal (Fig. 20.2)
CA125	14
Treatment given	Received six cycles of chemotherapy Hormone treatment: Provera 200 mg BD (had pulmonary embolism on provera), Anastrazole 1 mg OD

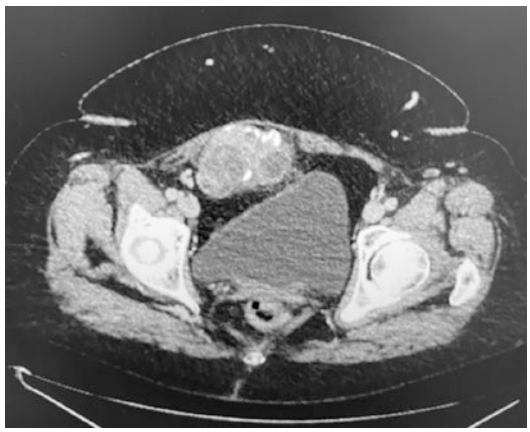


Fig. 20.2 A large heterogenous solid mass on the rectus sheath (arrow) indicating abdominal wall metastasis

Q: Discuss Management of this Case?

Grade 1 endometroid cancer of the uterus and ovary is an indolent disease and usually responds to hormone therapy. Immunohistochemistry of biopsy from recurrence is crucial to distinguish whether its recurrence of ovarian or uterine cancer. In this patient it is WT-1 negative so its likely to be a recurrence of corpus cancer.

Management of multisite recurrence remains systemic therapy with chemotherapy and hormone treatment and immunotherapy depending upon the molecular profile of this patient. Cytoreductive surgery is being increasingly adopted for recurrent endometrial cancer where it is feasible to obtain complete resection (R0). Surgery and radiotherapy per se have a role but likely to be palliative in nature.

Key Points

- Careful detailed work up and a multidisciplinary input is essential before embarking on treatment for recurrent endometrial cancer.
- Molecular profiling of the recurrent endometrial cancer has modified the systemic treatment options for these cases.
- Immunotherapy, chemotherapy and hormone therapy are recommended for multisite recurrences which are not surgically salvageable
- Surgery and radiotherapy still remain the mainstay for treatment for localized pelvic recurrences of endometrial cancers.

References

1. Del Carmen MG, Boruta DM 2nd, Schorge JO. Recurrent endometrial cancer. Clin Obstet Gynecol. 2011;54:266–77.
2. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van der Steen-Banasik E, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003;89:201–9.
3. Legge F, Restaino S, Leone L, Carone V, Ronsini C, Di Fiore GLM, Pasciuto T, Pelligra S, Ciccarone F,

Scambia G, et al. Clinical outcome of recurrent endometrial cancer: analysis of post-relapse survival by pattern of recurrence and secondary treatment. Int J Gynecol Cancer. 2020;30:193–200.
4. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, DiSilvestro P, Pearl ML, Argenta PA, Powell MA, et al. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG oncology/GOG0209). J Clin Oncol. 2020;38:3841–50.
5. Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, Barretina-Ginesta MP, Moreno V, Gravina A, Abdeddaim C, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol. 2020;6:1766–72.
6. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, Romeo M, Bratos R, Brose MS, DiSimone C, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol. 2020;38:2981–92.
7. Rütten H, Verhoef C, van Weelden WJ, Smits A, Dhanis J, Ottevanger N, Pijnenborg JMA. Recurrent endometrial cancer: local and systemic treatment options. Cancers. 2021;13:6275. https://doi.org/10.3390/cancers13246275.

Part IV

Case Based Studies: Gynaecological Sarcoma and Carcinosarcoma

21 Leiomyosarcoma, Endometrial Stromal Sarcoma, Undifferentiated Stromal Sarcomas, Adenosarcoma, Smooth Muscle Tumor of Unknown Malignant Potential

Bindiya Gupta and Kavita Singh

Introduction

WHO has classified uterine sarcomas as leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), adenosarcoma, rhabdomyosarcoma and perivascular epitheiloid cell neoplasm (PEComa). Leiomyosarcomas are the commonest (about two-third of the cases) followed by ESS (around 25%) and other rare histologies.

Leiomyosarcomas are aggressive sarcomas with characteristic pathological features of interlacing fascicles of spindle shaped tumor cells, coagulative necrosis, high mitotic rate, and significant cytologic atypia. Mitotic index is an important factor and cut off values of 10 mitoses/10 high-power fields, ≥4 mitoses/10 high-power fields, and ≥2 mitoses/10 high-power fields are used for the diagnosis of spindle, epithelioid, and myxoid uLMS, respectively [1]. Immuno-histochemical markers like smooth muscle markers, including desmin, h-caldesmon, histone deacetylase 8 (HDCA8) and smooth muscle actin along with positive p16, p53 and Ki67 expressions support the diagnosis of leiomyosarcomas. The main differential diagnosis on pathology are Smooth muscle tumor of unknown malignant potential (STUMP), cellular leiomyoma and myxoid leiomyoma.In uLMS, estrogen receptors (ER) has been reported to be positive in 25–60% of cases and progesterone receptors (PR) in 35–60% respectively [1].

According to World Health Organization (2014), endometrial stromal tumors (EST) are divided into four categories [2]. The most common is low grade endometrial stromal sarcoma (LG-ESS) followed by high grade endometrial stromal sarcoma (HG-ESS). The third categoryis undifferentiated uterine sarcoma (UUS) which has been labelled as a separate entity than HG-ESS. Both HG-ESS and UUS are together referred to as high grade sarcomas. The fourth type, endometrial stromal nodule (ESN), is rare and has a benign course.

ESN present as well circumscribed solitary nodule with no myometrial or lymphovascular invasion, low mitotic activity and minimal cytological atypia. These should be differentiated from LG-ESS and cellular leiomyomas. Low grade ESS may present as an endometrial polyp and may also occur at extrauterine sites especially in association with endometriosis. It has a tendency for lymphovascular invasion, and the wormlike or 'tongue-like' patterns of myometrial and lymphovascular invasion are classical histological features. Low grade ESSs are usually

B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_21

positive for ER, PR and CD10. HG-ESS is characterized by high mitotic activity and necrosis, and is negative for ER, PR and CD10 on immunohistochemistry but positive for cyclin D1 and c-kit. Unlike LG-ESS, HG-ESS are clinically more aggressive, have frequent extrauterine disease at presentation and have earlier and more frequent recurrences.

Undifferentiated uterine sarcoma, is a high-grade sarcoma that lacks the morphological and immunohistochemical characteristics of LMS and ESS and is generally a diagnosis of exclusion. These are large fleshy tumors with destructive infiltrative growth into uterine wall, have extensive hemorrhage, necrosis, mitotic activity and lymphovascular invasion. It does not express ER and PR, and is associated with a poor prognosis even for early stage disease, early recurrence and uncertain response to systemic treatment.

The 2014 classification has incorporated molecular classification of endometrial stromal tumors based on the profiling. This may be rarely used in cases of diagnostic dilemmas. Specifically, the JAZF1-SUZ12 (formerly JAZF1-JJAZ1) fusion identifies a large proportion of ESN and LG-ESSs, whereas the YWHAE-FAM22translocation identifies HG-ESSs [2].

Uterine adenosarcoma is a biphasic tumor composed of a benign epithelial component and a stromal component that is a low grade homologous uterine sarcoma. Adenosarcomas are considered to be of low malignant potential and generally have a favourable prognosis. If the sarcomatous part occupies more than 25% of the tumor volume, the situation is referred to as sarcomatous overgrowth and accounts for about 10% of cases which show aggressive clinical behavior. The epithelial component is positive for ER and PR, the sarcoma component shows positivity for CD 10. Presence of sarcomatous overgrowth and lymphovascular space invasion has been linked to increased recurrence (45–70%) [3].

Uterine carcinosarcomas are mixed histologies having bothmalignant epithelial and malignant stromal (sarcomatous) component and are now considered as high grade endometrial carcinomas.

Case 1: Uterine Leiomyosarcoma

Age, Parity, PS	76 years, P2 + 0 ECOG 1
Clinical presentation	Post menopausal bleeding × 5 months Blood stained vaginal discharge × 4 months Previous cervical smears regular and normal Examination: Highly suspicious friable growth seen through the external os −6 cm, uterus bulky, same growth felt through the cervical os, fornices free, no thickening in parametrium
Co morbidities	Glaucoma, hypertension, previous surgery for breast fibroadenoma
Transvaginal sonography	Uterus size 8 × 6 × 5 cm, endometrial thickness 6 mm, polypoidal mass in the lower part of uterus extruding through the cervix and vagina measuring 7 × 8 cm with increased vascularity
Cervical biopsy	Atypical spindle shaped cells, positive for Desmin, SMA, h-caldesmon suggestive of uterine Leiomyosarcoma (uLMS)
MRI	8.2 cm heterogenous mass showing areas of intermediate and high signal intensity arising from the lower uterine segment just above the cervix. No parametrial invasion. No enlarged pelvic or Para aortic nodes. Bilateral ovaries normal. Upper abdomen: Normal with no evidence of metastatic disease
Other investigations	CT chest: Normal
Surgery	Total abdominal hysterectomy+ bilateral salpingo oophorectomy
Intraoperative findings	Uterus bulky, lower segment ballooned up, large friable mass 8 × 9 cm arising just above the cervix from the lower uterine segment. Bilateral ovaries were normal. Rest of the pelvis and upper abdomen normal. Pelvic and paraaortic nodes not enlarged (Fig. 21.1)
Histology	Leiomyosarcoma, mitotic count >20/hpf, necrosis <50%, cervical stromal involvement present Parametrium normal, no LVSI, bilateral tubes and ovaries normal IHC: Desmin, SMA, caldesmon positive, CD10, S100, CD 17 negative, ER, PR negative FIGO stage 1B

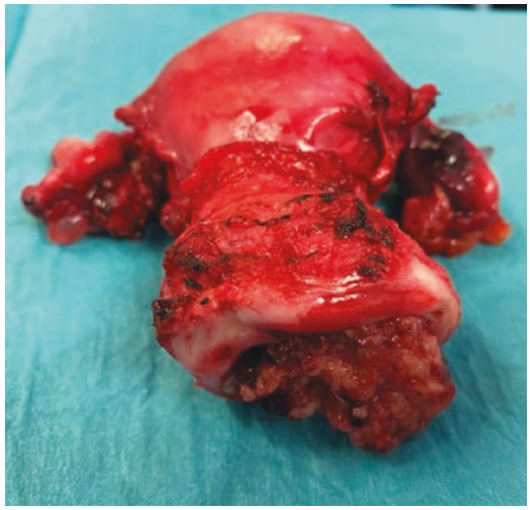


Fig. 21.1 Uterus bulky, lower segment ballooned up, large friable mass 8 × 9 cm arising from lower uterine segment protruding from cervix; HPE: leiomyosarcoma

Q: Describe the Pre Operative Work Up in uLMS?

A rapidly growing solitary uterine mass in the postmenopausal woman arises a strong suspicion of uterine sarcoma. Presence of heavy menstrual bleeding with anemia further raises clinical suspicion of presence of a sarcoma. Endometrial sampling is positive in around 50% of patients with uLMS. Cross-sectional imaging is performed to assess the size of the uterine mass and delineate its operability and exclude metastasis. All imaging has its limitations in having low specificity and sensitivity for differentiating sarcomas from degenerating fibroids. However, diagnosis of degenerating fibroids has to be taken with caution in a postmenopausal woman. Diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) have improved the MRI assessment of indeterminate myometrial mass with a sensitivity of 88% and a specificity of 96%. The coagulative necrosis present in uLMS, presents as an area of central non-enhancement on MRI, as opposed to the scattered areas of non-enhancement present in leiomyomas with degeneration [4].

Abdomino-pelvic MRI helps to assess any parametrial extension, spread to adjacent pelvic structures and lymph nodes metastasis. CT Chest is essential to exclude metastasis to lungs as sarcomas are notorious for hematogenous spread and metastasizing to lungs. PET CT scan may have a role in excluding distant metastasis. Few studies have shown a typical FDG uptake pattern, "hollow ball sign" which identifies the presence of tumor necrosis, may help in distinguishing uLMS from leiomyomas [5].

Q: What Is the Management Plan?

The management is decided in a multi disciplinary tumor board (MDT) meeting or a designated regional sarcoma MDT. Links to the sarcoma MDT should be maintained to ensure that patients are appropriately registered, managed, considered for clinical trials, and referred for systemic treatment if required for metastatic disease.

Since the disease is confined to uterus, intact, "en bloc" surgical resection of the tumor with negative pathologic margins is the gold standard primary therapy. This includes a total abdominal hysterectomy +/− bilateral salpingo-oophorectomy with biopsy of any suspicious lesions [6]. The specimen should be delivered intact and should not be bisected or morcellated and intraoperative spillage should be avoided. In case extrauterine disease is detected intraoperatively, maximum cyto reduction should be done whenever possible.

Detailed counselling should be done explaining that surgery is the definitive treatment for the patient. The surgical procedure and its complications like bladder or bowel injury, need for blood transfusion, infection, thrombosis and embolism should be explained. She should be counselled that although the disease is confined to uterus, confirmation would be done only after final histopathology and there may be a need for adjuvant chemo/ radiotherapy if disease is upstaged on surgery and final histopathology. Prognosis of the tumor should be also explained to the patient.

Q: What Is the Percentage of Lymph Node Metastasis and Role of Lymphadenectomy? Role of Ovarian Conservation in uLMS

The rates of lymph node involvement in uLMS has been reported to be 3–11%. The role of routine pelvic lymphadenectomy is not clearly established for uterine sarcomas as it does not affect overall survival. However, bulky nodes should be resected for maximum cytoreduction [7].

Ovarian metastasis is seen in less than 5% of patients and iatrogenic surgical menopause following oophorectomy may impact cardiovascular health, bone density, and life expectancy and clinicians may consider preserving normal appearing ovaries especially in premenopausal women [8]. As not much evidence is available in literature, this decision is recommended only after an individualized assessment of the case and appropriate counseling. Even if a decision of ovarian conservation is made, a prophylactic salpingectomy is recommended. In postmenopausal women it is preferable to perform bilateral salpingo-oophorectomy.

Q: Role of Adjuvant Treatment in Stage 1 uLMS?

Studies have shown no significant difference in local or distant recurrence rates, or overall survival with use of adjuvant radiotherapy or chemotherapy in early stages. The EORTC (European Organisation for Research and Treatment of Cancer) trial 55874, a randomized trial, concluded that adjuvant radiation therapy did not improve loco- regional relapses (20% with RT versus 24% without RT) or distant failure rates and had no effect on overall survival (OS) in patients with uLMS [9]. Due to the lack of proven benefit, coupled with the toxicity associated with chemotherapy and radiation, adjuvant therapy cannot be universally recommended for women with non-morcellated, completely resected stage I disease and they are kept under close surveillance [10]. It can be discussed on a case to case basis as retrospective data shows improved local control and prolongs recurrence free survival with adjuvant radiotherapy in high risk cases like grade 2,3; stage 1B tumours [11].

Q: Follow Up Protocol

Recurrence most commonly occur in the first 2 years, hence surveillance is more intensive in the first 2 years. Post treatment surveillance protocol is suggested as follows [12]:

(a) History and physical examination 3–4 monthly first 2–3 years, then 6–12 monthly × 3 years. Patient should be educated regarding symptoms of recurrent disease like vaginal or rectal bleeding, weight loss, pain in pelvis, abdomen, backache, cough and limb edema.
(b) Imaging surveillance: Chest/ abdominal and pelvic CT scan every 6 months first 2 years and then annually for next 3 years. PET/CT can be used in when there is a suspicion of distant metastasis

Q: What Is the Treatment for Advanced Stage uLMS?

Surgical cytoreduction with the goal of no gross residual disease is recommended in advanced cases and recurrent masses amenable to surgery. Due to increased risk of relapse, adjuvant chemotherapy with or without radiotherapy may be considered in completely resected Stage II and above uLMS. RT needs to be individualized after a multidisciplinary evaluation depending upon the histopathological findings like cervical, serosal or parametrial involvement, balancing the risk of relapse, patient performance status and side effects.

Chemotherapy has demonstrated improved survival in women with advanced stage disease (stage II-IV) and may also be considered in selected cases with higher risk of recurrence like

tumor morcellation done during surgery in stage I disease. Single agent doxorubicin or combination of gemcitabine with docetaxel is preferred as first line adjuvant therapy [13]. Doxorubicin (75 mg/m^2) is given intravenously and repeated 3 weekly [12, 14]. A combination of gemcitabine with docetaxel has an overall response rate of 40%, and it can be used for first line treatment [15]. Gemcitabine 900 mg/m^2 over 90 min followed by Docetaxel 100 mg/m^2 over 60 min on day 8 repeated three weekly [12]. Olaratumab (monoclonal antibody acting on PDGFRα) in combination with doxorubicin have shown improved overall survival (26.5 months versus 14.7 months) and is recommended by NCCN in advanced cases [16]. It is also FDA approved in patients with unresectable disease activity in uLMS [17].

Multiagent therapy with a combination of doxorubicin, ifosfamide, cisplatin and RT had improved 5 year PFS (51% versus 29% with RT alone) but had significantly high toxicity [18]. There is lack of literature regarding the role of chemotherapy in neoadjuvant settings; hence, no definitive recommendations can be made [10]. Other second line options are Dacarbazine, Epirubicin, Eribulin, Gemcitabine, Ifosfamide, Liposomal doxorubicin as single agents or alone in combination [11].

Hormone therapy including aromatase inhibitors (e.g. Anastrazole) and systemic progestins may show potential benefit in ER, /PR positive uLMS in adjuvant settings especially in advanced stages [19]. Tamoxifen is not recommended due to its pro-estrogenic actions. Use of oestrogen-lowering therapies should be used with particular caution in patients with high-grade rapidly progressing tumours.

Biologic and targeted therapies have been the focus of recent studies.Trabectedin an alkaloid can be added to Doxrubicin with a good disease control around 87%. with acceptable tolerability and side effect profile [20]. The benefit of the drug in controlling the disease beyond six cycles of combination chemotherapy has been studies and is found promising (HR 0.58) [21]. Role of bevacizumab and multikinase inhibitor like sunitinib and sorafenib is not ascertained.

Q: Treatment of Recurrent/Metastatic uLMS?

A complete assessment of loco-regional relapse and distant metastasis should be done on imaging (MRI abdomen and pelvis + CT Chest). Patient assessment of operability and performance status should be done and along with detailed counselling.

Surgery should be considered in recurrent or oligo-metastatic cases in women with a good performance status especially if there has been a relatively long disease-free interval and the sites of recurrence are amenable to optimal cytoreduction. Resection of isolated pulmonary metastases, both at initial diagnosis and at the time of recurrence, is also associated with improved survival.

Adjuvant chemo therapy and or Radiotherapy (EBRT+/− Brachytherapy) is offered after initial treatment. In case surgical resection is not feasible, palliative chemotherapy or hormone therapy in receptor positive cases is given. Pazopanib (tyrosine kinase inhibitor) can be used as salvage treatment in refractory settings [22]. Biomarker directed systemic therapy like Anti – PD1 antibody like Nivolumab and Pembrolizumab can be used as salvage treatment in tumours positive for PD1 [6, 12]. Other options include PARP inhibitors in BRCA −2 altered ULMS andLarotrectinib or entrectinib for NTRK gene fusion positive tumours [12]. Anti- CD 47 monoclonal antibodies are under investigation [6].

Q: What Are the Prognostic Markers of Leiomyosarcoma?

Stage of disease at time of diagnosis is the single most important prognostic factor. Five-year survival is around 75% with stage I disease and around 60% for women with stage II disease. Those with metastatic disease have much lower survival rates, around 10–15% at 5 years. Recurrence is high upto 50–60%. The most common site of first recurrence is lungs (40%) and the median time interval for recurrence is

estimated around 12–24 months. Other prognostic features include advanced age at diagnosis, large tumor size, cervical involvement and high mitotic index. Leiomyosarcomas are not graded as there is no correlation between higher grade and survival outcomes. Some studies have shown that expression of ER and PR receptors >10% is associated with favourable prognosis.

Q: Management of uLMS Diagnosed After Hysterectomy Done for Benign Fibroid?

All these cases must be evaluated by the institutional MDT. In such cases, details of surgery should be obtained and reviewed with special emphasis on type of hysterectomy (total/ subtotal), intraoperative morcellation, tumor fragmentation and removal of ovaries. Expert pathological review should be done. Contrast enhanced CT chest and MRI abdomen and pelvis should be done to exclude residual and metastatic disease. PET-CT may be used in case CT findings are equivocal and not confirmatory.

Surgical exploration and complete resection is the preferred option in case of any gross residual disease on imaging. In cases where morcellation was used, surgical re-exploration along with chemotherapy may be considered. In case the patient is not suitable for primary surgery, chemotherapy and/or radiotherapy can be given.

Q: What Are the Current Guidelines for Morcellation in Uterine Fibroids and How Does It Affect the Prognosis in an Occult uLMS?

Morcellation of uterine tumors is associated with dissemination of malignant tumor, worse survival outcomes and increased risk of recurrence. Studies have shown that the disease-free survival and overall survival significantly reduced from 65% to 40% and 73% to 46% after morcellation respectively [6].

U.S. Food and Drug Administration (FDA) issued a safety communication in 2014 warning against the use of electromechanical morcellators during most surgeries for fibroids. FDA further issued a “black box” warning in November 2014 for labeling all electromechanical morcellators which highlighted the risks associated with electromechanical morcellation.

Several laparoscopic and gynecological societies after reviewing evidence developed guidelines suggesting restrictive use e.g. avoidance in post menopausal women, cases with suspicion or proven malignancy, in bag morcellation, careful preoperative assessment and counselling [23]. However, decision should be individualized and extensive counselling and informed consent must be taken from all the patients highlighting the possibility of an occult malignancy.

Q: Role of Hormone Replacement Therapy (HRT) After Treatment of uLMS?

Uterine leiomyosarcomas often express estrogen and progesterone receptors, hence hormone replacement may stimulate growth of microscopic residual disease. However, ovarian preservation has shown no affect on survival in many studies. Not much evidence is available and use of hormone replacement therapy is controversial; much caution should be taken and extensive counselling should be done before using hormone therapy (Table 21.1).

Case 1

Patient is on a regular follow up for last 3 years and there has been no recurrence.

Table 21.1 FIGO Staging System for Uterine Leiomyosarcomas and Endometrial Stromal Sarcomas (2009)

Stage	Definition
I	Tumor limited to uterus
IA	Tumor size less than or equal to 5 cm
IB	Tumor size more than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor involves abdominal tissues
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or Para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Case-2: Low Grade Endometrial Stromal Sarcoma

Age, Parity, PS	42 years, P2 + 0, previous 2 LSCS PS = 0
Clinical presentation	Heavy menstrual bleeding with passage of clots × 8 months Foul smelling vaginal discharge × 8 months Increased urinary frequency × 4 months Previous history of myomectomy 8 years back, histopathology report: Leiomyoma Previous cervical smears regular and normal Examination: Uterus enlarged to 14 weeks, restricted mobility, fornices free, no thickening in parametrium
Co morbidities	Borderline diabetes, hypertensive controlled on amlodipine 5 mg OD
Transvaginal sonography	Mass in the uterine cavity 9 × 8 × 8 cm, with heterogeneous echoes mildly increased vascularity. Endometrial thickness: 25 mm. Bilateral adnexa were normal. Impression: Submucus fibroid with endometrial hyperplasia
Endometrial biopsy	Atypical endometrial hyperplasia
Surgery	Total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolicomentectomy, removal of nodules from the peritoneum
Intraoperative findings	Uterus 12–14 weeks, 6 × 7 cm mass fleshy inside the endometrial cavity (Fig. 21.2). Multiple solid fleshy nodules were present in the omentum, peritoneum. One exteranal iliac node enlarged on the right side, removed. Rest of the pelvic and paraaortic lymph nodes were not enlarged
Histology	Large cellular tumor centered o upper anterior uterine wall with no demonstrated serosal breach and no involvement of cervix appearance suggestive of LG-ESS with extensive LVSI. Parametria, fallopian tube and ovaries free of tumor IHC: diffusely positive CD10 and WTI, diffuse and strongly positive for ER and PR (Allred score 8/8) omental nodules and peritoneal nodules showing metastasis from tumor. External iliac lymph node negative FIGO stage 3 B

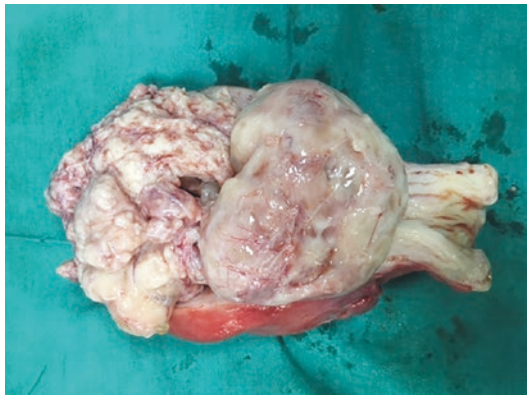


Fig. 21.2 Uterus 12–14 weeks, 6 × 7 cm mass fleshy inside the endometrial cavity; HPE: endometrial stromal sarcoma low grade

Q: What Is the Recommended Surgical Treatment for LG –ESS?

Since, LG-ESS is a hormonally responsive tumor, total abdominal hysterectomy, with bilateral oophorectomy is treatment of choice. There is usually no role of ovarian preservation but in women wishing for fertility conservation and stage 1a disease ovaries can be preserved after extensive counsellig [24]. Complete cytoreduction is recommended in advanced tumors with extrauterine manifestations. Routine lymphadenectomy is usually not advised as involvement of the pelvic and para-aortic lymph nodes does not appear to have any influence on overall survival. Removal of bulky lymph nodes is a part of complete cytoreduction [25].

For recurrent or metastatic disease, complete surgical resection is associated with an increased rate of cure and prolonged survival. Due to the slow growth of the lesions, ESS can also be repeatedly successfully resected after each recurrence.

Q: Role of Hormone Therapy in LG-ESS? How Does Histological Expression of Steroid Receptors Guide Response To Hormonal Treatment?

Hormonal therapy (estrogen blockade) is used as adjuvant treatment in advanced stages (stages II-IV) and for recurrent, non resectable or metastatic LG-ESS lesions.

On histology, the immunohistochemical expression of estrogen and progesterone receptors is estimated using the Allred score.

Aromatase inhibitors (AI) including anastrazole (1 mg/day) are used as first line hormone therapy. Type I AIs like Exemestane are steroidal inhibitors and bind to aromatase irreversibly by covalent bonds while type 2 AIs bind like letrozole, anastrazole bind with aromatase reversibly [22]. In patients with advanced and recurrent disease the clinical benefit rate is 92% with 2 year PFS of 89% [26]. Second line options include Progestins (Megestrolacetate 160–320 mg/day, Medroxyprogesterone acetate (200–600 mg/day) and occasionally Gonadotropin releasing hormone have also been used in these cases. Tamoxifen is contraindicated as it may have some pro-estrogenic effect. While some oncologists prefer 2 years of hormonal treatment, others are inclined to give it lifelong. Mammalian target of rapamycin (mTOR) inhibitors like sirolimus which can reverse hormone resistance, can also be added to the regimen. The common side effects of progesterone therapy include weight gain, bloating, leg edema, water retention and breast tenderness. If the symptoms are severe aromatase inhibitors can be given. Common side effects of anastrazole include bone pains, blurred vision, chest pain or discomfort, dizziness, headache, swelling of the feet or lower legs.

Chemotherapy (doxorubicin and ifosfamide) can be given in patients following recurrence in previously treated patients with hormones, or when hormone therapy is no longer an option due to side effects.

Q: Role of Post Operative RT in ESS?

Use of adjuvant radiation has limited clinical value in LG-ESS and may be associated with better locoregional control without an impact on OS. Hence for early stage disease radiation should be added on a case to case basis.

Adjuvant External beam radiotherapy (EBRT) may be added along with hormone therapy in stage II-IVA. The decision should depend on case

to case basis depending on histologic features like pelvic and cervical extension. In IVB disease palliative RT may be used additionally along with estrogen blockade.

Q: What Is the Follow Up Protocol?

The risk of recurrence in LG-ESS is 10–20%, and late recurrences after more than 10–30 years are characteristic of the disease. The follow up protocol is similar to LMS as mentioned above, however, a longer duration probably a life long follow up is required in LG -ESS.

Q: What Is the Prognosis of LG- ESS?

Forty percent of recurrences are locoregional while 60% are distant metastases. Median time of recurrence is 5–10 years in stage I and II while in stage III and IV majority are seen in 1 year. Tumor stage is the most important prognostic factor. The 5-year OS for Stage I patients is more than 90%, but decreases to 50% for Stage III and IV.

Q: What Is the Management of High Grade ESS?

High grade ESS are hormone receptor negative, aggressive tumors, with earlier and frequent recurrence and poor survival. The 5-year OS rate for FIGO Stage IA and FIGO Stage IB HG-ESS is 51.4% and 43.5%, respectively. Surgery with complete cytoreduction is the mainstay of treatment [22]. Adjuvant chemotherapy may be used in stage II-IV disease taking into account the high risk of recurrence. Chemotherapy regimens in HG-ESS include carboplatin and paclitaxel; doxorubicin and ifosfamide; doxorubicin, ifosfamide and cisplatin; doxorubicin, vincristine and cyclophosphamide; and oral etoposide. Evidence has shown improved PFS and OS with post operative pelvic RT with or without brachytherapy; hence adjuvant RT may be considered appropriate in stage II and beyond [27].

Case 2

Post operative CECT Chest, abdomen and pelvis was done to exclude other metastasis and was normal.

The patient is on a regular follow up. Patient is currently on Provera 200 mg/day as adjuvant therapy.

Case 3: Adenosarcoma

Age, Parity, PS	84 years, Mrs. P, P3 + 0
Clinical presentation	Post menopausal bleeding × 6 months, attained menopause at 50 years Blood stained discharge × 4 months No history of weight loss, loss of appetite, no bowel or urinary complaints
Co morbidities	Hypertensive, diabetic on Linagliptin 5 mg/day, Ramipril and atorvastatin
Transvaginal sonography	Bulky uterus, mass in the endometrial cavity-8 cm, bilateral ovaries normal
Endometrial biopsy	? Spindle cells with mild nuclear atypia, occasional mitosis, necrosis? Adenosarcoma
MRI	Bulky uterus 12 × 8 cm, distorted uterine cavity filled with solid mass with restricted diffusion on DWI. More than 50% myometrium involved. No cervical stromal invasion. Bilateral ovaries atrophic. No pelvic and retroperitoneal lymphadenopathy. Cystic lesions in pancreas, rest normal. Non specific small nodule in left lower lung
CT chest	Non significant lesion in the lung
Surgery	Total abdominal hysterectomy with bilateral salpingo-oophorectomy, omental biopsy
Histology	Uterus- uterine adenosarcoma with sarcomatous overgrowth, outer half myometrial invasion, serosal involvement absent, tumor free distance to uterine serosa: 4 mm, no LVSI, cervical and parametrial involvement absent. No malignancy in adenexa and omentum FIGO stage IC

Q: What Is the Initial Work Up and Staging for Adenosarcoma?

Like all sarcomas, cross sectional imaging using diffusion weighted MRI of abdomen and pelvis is recommended. MRI is useful to assess the size of tumor, myometrial invasion, involvement of retroperitoneal lymph nodes and presence of extrauterine disease. CT Chest should be done to rule out lung metastasis. Adenosarcoma is diagnosed on endometrial curettage in 25% cases.

Q: What Is the Prognosis of Adenosarcoma?

Adenosarcoma is a tumor of low malignant potential and recurrence rates are between 15–25% after treatment completion. However, presence of sarcomatous overgrowth is associated with higher rates of recurrence (45–70%) and high mortality (up to 75%). Other prognostic factors include age, extrauterine disease, lymph node involvement, myometrial and lymphovascular space invasion [28]. The 5-year survival rate for stage I is 70–80% while it is 50% for stage III disease [29]. The patient has high risk factors like sarcomatous overgrowth and deep myometrium invasion, hence needs to be counselled that there is a higher risk of recurrence.

Q: What Is the Treatment for Adenosarcoma?

Standard treatment includes hysterectomy with or without removal of the ovaries. Recommendation on removal of ovaries is not very clear as evidence on its relation to survival and relapse is lacking. Removal of ovaries is justified in perimenopausal and postmenopausal age group while in younger women they may be conserved after extensive counselling. In patients with advanced disease, all attempts are made to achieve a maximum surgical debulking.

The role of lymphadenectomy is controversial. The incidence of lymph node metastasis is around 3% in various studies, and there is no data that removal of lymph nodes has any impact on overall survival [30]. Factors associated with increased likelihood of lymph node involvement include deep myometrial invasion, large tumor and sarcomatous overgrowth.

Role of routine adjuvant treatment in a completely resected disease, in patients who do not have high risk factors is not yet ascertained [3]. However, patients at high risk of disease recurrence may be considered for adjuvant chemotherapy. No survival benefit has been demonstrated with use of adjuvant RT.

For recurrent or metastatic disease, complete surgical resection remains the first choice of treatment and has shown a considerable impact on overall survival. Chemotherapy with doxorubicin and ifosfamide, Trabectedinand hormone therapy has also been employed successfully in a number of cases with relapsed adenosarcoma [27].

Palliative hormonal treatment like medroxyprogesterone acetate 200 mg/day or megesterol acetate 160 mg/day and aromatase inhibitors (e.g. anastrazole 1 mg/day) may be considered in adenosarcoma without sarcomatous overgrowth in hormone receptor positive tumors.

Case 4 Undifferentiated Uterine Sarcoma

Age, Parity, PS	59 years, P2 + 0, PS = 2
Clinical presentation	Heavy bleeding with passage of clots, severe anemia (6 g%) Not responsive to conservative management
Co morbidities	Type 2 diabetes on metformin
Transvaginal sonography	Bulky uterus, single mass indenting the endometrial cavity-5 cm, bilateral ovaries normal s/o submucs fibroid
Surgery	Underwent emergency TAH + BSO
Histology	Histopathology: Undifferentiated uterine sarcoma, involvement of serosa, cervix, extensive LVSI, no epithelial component to disease. Features not suggestive of carcinosarcoma, LMS, or ESS Provisional stage: 1B

Q: What Is the Management of UUS?

The standard management for UUS consists of total hysterectomy and bilateral salpingo-oophorectomy. The role of systematic lymphadenectomy is unknown and it is not recommended unless there is a clinical or radiological suspicion of nodal involvement. In this patient the diagnosis was made post operatively but the patient has all the risk factors like postmenopausal age, heavy bleeding with anemia and solitary uterine mass, hence the decision was taken for an emergency open hysterectomy and all precautions were taken to prevent intraoperative spillage.

In advanced disease, cytoreduction is recommended if feasible.

Adjuvant pelvic radiotherapy with or without brachytherapy may be given in advanced stages and recurrent disease. Postoperative ChT may be considered appropriate in advanced stages taking into account the high risk of recurrence. These are highly aggressive tumours with poor prognosis.

Case-4

Post op wound infection, healed in 2 weeks, Planned for adjuvant radiotherapy.

Post Operative (Day 14) CT scan abdomen + pelvis: no lymphadenopathy/ metastatic disease.

One month post surgery: increased fatiguability, loss of apetite, pain abdomen and bloating.

Hemoglobin: 43 g/l; received two blood transfusions Hb: 90 g/l.

Repeat CT TAP: Extensive bilateral lung metastasis and multiple metastatic deposits in abdomen.

Biomarkers: negative for PD1.

Plan: Palliative chemotherapy.

Case 5: Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP)

Age, Parity, PS	35 years, P1 + 0, PS-1
Clinical presentation	Progressive distension of abdomen with pain abdomen x6 months. Frequency of micturition × 1 month Menstrual cycle normal Examination 28 weeks abdomino pelvic mass arising from uterus firm to cystic in consistency
Co morbidities	Nil
Transvaginal sonography	Solid cystic mass arsing from uterus 16 × 20 cm, with increased internal vascularity. B/L ovaries normal, endometrial thickness: 10 mm
Endometrial biopsy	Proliferative endometrium
CECT abdomen + pelvis	Poorly defined large abdominopelvis complex cystic mass arising from anterior surface of uterus with minimal ascites. Bilateral ovaries visualized normal. No evidence of disease elsewhere. No enlarged lymph nodes
Surgery	Total abdominal hysterectomy with left salpingo oophorectomy and right salpingectomy
Histology	Solid areas composed of whorls of smooth cells showing pleomorphism mild to moderate atypia, mitotic count <5/10 HPF]. No area of necrosis s/o STUMP (Fig. 21.3)

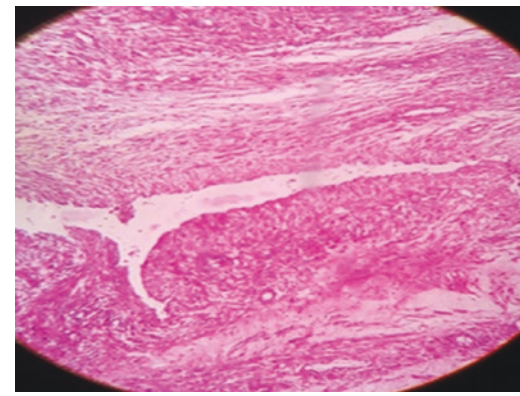


Fig. 21.3 STUMP: no area of necrosis, mitotic figures 4/10 hpf

Q: Clinical Presentation, Pathological Diagnosis and Management of STUMP

The mean age at presentation of STUMP is 10 years younger to LMS and the clinical presentation resemble uterine leiomyoma which includes features such as abnormal vaginal bleeding, abdominal pain, abdominal mass, pressure symptoms and anaemia.

The mainstay of diagnosis is pathological. According to WHO criteria the various combinations have been proposed of presence of necrosis, moderate to severe atypia and mitotic count to diagnose as STUMP. For histologic diagnosis, Mitotic count is less than 10/10 high power field; atypia is focal, multifocal or diffuse with absent necrosis or there is no or mild atypia if necrosis is present [31].

The treatment of choice is hysterectomy with or without ovarian conservation. There is no need of adjuvant treatment but a close follow up is required. Recurrence rates range between 7–28% which are similar to original tumours or are leiomyosarcoma. Immunohistochemical markers like p16, Ki 67 and p53 and presence of necrosis help in prognosis.

Table 21.2 summarizes the characteristics of different types of uterine sarcomas.

Table 21.2 Uterine sarcomas: Summary of characterstics, management & outcomes

	Leiomyosarcoma (uLMS)	Low grade Endometrial stromal Sarcoma (ESS)	High grade ESS	Undifferentiated Uterine sarcoma (USS)	Uterine adenosarcoma
Pathological features	Coagulative necrosis, mitosis, cytological atypia	Tongue like patterns of myometrial and lymphatic invasion	High mitotic activity, necrosis	Hemorrhage, necrosis, mitosis++, diagnosis of exclusion	Biphasic (epithelial+low grade sarcoma) >25% sarcoma component: sarcomatous overgrowth
Immuno Histochemistry	Desmin, SMA, h-caldesmon positive ER (25–60%) PR (35–60%)	ER+, PR + ve CD10 + ve	Cyclin D1, c-kit+ve ER,PR,CD10 negative	ER, PR negative	CD10 + ve in sarcoma ER, PR + ve in epithelial component
Treatment[a] (surgery is first line of treatment)	TAH+/-BSO Complete cytoreduction in advanced disease; preferred in recurrent and metastatic disease	TAH with BSO Complete cytoreduction in advanced disease; preferred in recurrent and metastatic disease	TAH with BSO Complete cytoreduction in advanced disease	TAH with BSO Complete cytoreduction in advanced disease	TAH+/-BSO Complete cytoreduction in advanced disease; preferred in recurrent and metastatic disease
Chemotherapy	Advanced stage (II-IV), recurrent, metastatic disease First line: Doxrubicin Second line: Doctaxel+gemcitabine	Recurrent disease on hormone therapy	Advanced stage (II-IV), recurrent, metastatic disease	Advanced stage (II-IV), recurrent, metastatic disease	Advancedstages+/– Recurrent/ metastatic disease
Hormone therapy[b] (response can be predicted using Allred score)	Hormone positive uLMS	Advanced stage (II-IV), recurrent, metastatic disease	–	–	+/– ER/PR positive epithelial tumor

Table 21.2 (continued)

	Leiomyosarcoma (uLMS)	Low grade Endometrial stromal Sarcoma (ESS)	High grade ESS	Undifferentiated Uterine sarcoma (USS)	Uterine adenosarcoma
Radiotherapy	May be considered in advanced stages. Case to case basis	EBRT may be considered in advanced stages, palliative RT in metastatic	May be considered in advanced stages	May be considered in advanced stages	No definite role
Other treatment[c]	Trabectedin Olaratumab				
Prognosis[d]	5- year OS: Stage 1: 75% Stage 2: 60% Metastatic disease: 10–15%	5-year OS: Stage 1: 85–90% Stage 3 and 4: 50% Late recurrence (10–30 years) common. Longer follow up required	Poor prognosis 40–50% survival early stage	Poor prognosis 50% survival early stage	Low malignant potential Recurrence rates 15–25% after treatment completion. Sarcomatous overgrowth (45–70%) recurrence

[a]No role of routine lymphadenectomy
[b]First line: aromatase inhibitor, second line: progestins; tamoxifen contraindicated
[c]Targeted therapy like Pazopanib, immunotherapy like temzolomideetc in recurrent/metastatic settings under trial
[d]Tumor stage most important prognostic factor

Key Points

- Uterine sarcomas are a relatively rarer group of uterine cancers.
- Surgery is the cornerstone of treatment, even in advanced, recurrent and oligo-metastatic cases.
- Surgical specimen should be removed intact and morcellation is contraindicated.
- Hormone therapy is used in LG –ESS, hormone receptor positive uLMS, select cases of adenosarcoma.
- The current role of chemotherapy is in advanced, recurrent and unresectable uLMS, HG-ESS and UUS. Gemcitabine / Docetaxel and Doxorubicin are the most active regimens.
- Stage at diagnosis is the strongest predictor which determines the survival.
- But even with the current cytotoxic regimens, the 5-year disease-specific survival remains low, often less than 30%.

References

1. Longacre TA, Lim D, Parra-Herran C. Leiomyoscaroma. In: Kurman RJ, Carcangiu ML, Herrington CS, editors. WHO classification of tumours female genital tumors, vol. 4. 5th ed. Lyons: IARC Press; 2020. p. 283–6.
2. Conklin CM, Longacre TA. Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol. 2014;21(6):383–93.
3. Ulrich UA, Denschlag D. Uterine adenosarcoma. Oncol Res Treat. 2018;41(11):693–6.
4. Sun S, Bonaffini PA, Nougaret S, Fournier L, Dohan A, Chong J, Smith J, Addley H, Reinhold C. How to differentiate uterine leiomyosarcoma from leiomyoma with imaging. Diagn Interv Imaging. 2019;100(10):619–34.
5. Ho KC, Dean Fang YH, Lin G, Ueng SH, Wu TI, Lai CH, Chueh HY, Chao A, Chang TC, Yen TC. Presurgical identification of uterine smooth muscle malignancies through the characteristic FDG uptake pattern on PET scans. Contrast Media Mol Imaging. 2018;2018:7890241.
6. Roberts ME, Aynardi JT, Chu CS. Uterine leiomyosarcoma: a review of the literature and

update on management options. Gynecol Oncol. 2018;151(3):562–72.
7. Si M, Jia L, Song K, Zhang Q, Kong B. Role of lymphadenectomy for uterine sarcoma: a meta-analysis. Int J Gynecol Cancer. 2017;27(1):109–16.
8. Leitao MM, Sonoda Y, Brennan MF, Barakat R, Chi DS. Incidence of lymph node and ovarian metastasis in leiomyosarcoma of the uterus. Gyncol Oncol. 2003;91(1):209–12.
9. Reed NS, Mangioni C, Malmström H, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008;44:808–18.
10. Hensley ML, Barrette BA, Baumann K, Gaffney D, Hamilton AL, Kim JW, Maenpaa JU, Pautier P, Siddiqui NA, Westermann AM, Ray-Coquard I. Gynecologic Cancer InterGroup (GCIG) consensus review: uterine and ovarian leiomyosarcomas. Int J Gynecol Cancer. 2014;24(9 Suppl 3):S61–6.
11. Ref from retrospect
12. NCCN Guidelines Version 1.2020. Uterine sarcoma. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed 14 May 2022.
13. Kyriazoglou A, Liontos M, Ntanasis-Stathopoulos I, Gavriatopoulou M. The systemic treatment of uterine leiomyosarcomas: a systematic review. No news is good news? Medicine (Baltimore). 2021;100(13):e25309.
14. Sutton G, Blessing J, Hanjani P, Kramer P, Gynecologic Oncology Group. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 2005;96(3):749–52.
15. Hensley ML, Ishill N, Soslow R, Larkin J, Abu-Rustum N, Sabbatini P, Konner J, Tew W, Spriggs D, Aghajanian CA. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: results of a prospective study. Gynecol Oncol. 2009;112(3):563–7.
16. Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016;388(10043):488–97.
17. Olaratumab (LARTRUVO) FDA. 2016. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm526087.htm. Accessed 29 April 2022.
18. Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Ann Oncol. 2013;24(4):1099–104.
19. Zang Y, Dong M, Zhang K, Gao C, Guo F, Wang Y, Xue F. Hormonal therapy in uterine sarcomas. Cancer Med. 2019;8(4):1339–49.
20. Pautier P, Floquet A, Chevreau C, Penel N, Guillemet C, Delcambre C, et al. French Sarcoma Group. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol. 2015;16(4):457–64.
21. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34(8):786–93.
22. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879–86.
23. Tissue Extraction Task Force Members. Electronic address: generalmail@aagl.org. Morcellation during uterine tissue extraction: an update. J Minim Invasive Gynecol. 2018;25(4):543–50.
24. Horng HC, Wen KC, Wang PH, Chen YJ, Yen MS, Ng HT. Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma Part II-Uterine endometrial stromal sarcoma: The TAG systematic review. Taiwan J Obstet Gynecol. 2016;55(4):472–9; TAg Review.
25. Barney B, Tward JD, Skidmore T, Gaffney DK. Does radiotherapy or lymphadenectomy improve survival in endometrial stromal sarcoma? Int J Gynecol Cancer. 2009;19(7):1232–8.
26. Thanopoulou E, Aleksic A, Thway K, Khabra K, Judson I. Hormonal treatments in metastatic endometrial stromal sarcomas: the 10-year experience of the sarcoma unit of Royal Marsden Hospital. Clin Sarcoma Res. 2015;5:8.
27. Benson C, Miah AB. Uterine sarcoma - current perspectives. Int J Womens Health. 2017;9:597–606.
28. Nathenson MJ, Conley AP. Prognostic factors for uterine adenosarcoma: a review. Expert Rev Anticancer Ther. 2018;18(11):1093–100.
29. Nathenson MJ, Ravi V, Fleming N, Wang WL, Conley A. Uterine adenoscarcoma: a review. Curr Oncol Rep. 2016;18(11):68.
30. Machida H, Nathenson MJ, Takiuchi T, et al. Significance of lymph node metastasis on survival of women with uterine adenosarcoma. Gynecol Oncol. 2017;144:524–30.
31. IpPPC, Croce S, Gupta M. Smooth muscle tumor of uncertain malignant potential of the uterine corpus. In: Herrington CS, editor. WHO classification of tumours female genital tumors, vol. 4. 5th ed. Lyons: IARC Press; 2020. p. 279–80.

22 Carcinosarcoma of the Mullerian Tract: Uterine, Ovarian, Fallopian Tube

Kavita Singh and Bindiya Gupta

Introduction

Carcinosarcomas (CS) also known as malignant mixed mullerian tumours (MMT) are biphasic tumours having both malignant epithelial and sarcomatous component of monoclonal origin. Epithelial component may be endometrioid, clear cell or serous while sarcomatous component may be homologous or heterologous. The homologous components may include endometrial stromal sarcoma, undifferentiated sarcoma, fibrosarcoma, leiomyosarcoma or their combination while heterologous elements are usually rhabdomyosarcoma and chondosracoma. These are highly aggressive tumours and clinical course is similar to high grade endometrial carcinomas. Based on clonality studies CS are now regarded as metaplastic carcinomas and they arise from the carcinoma lineage. These are no longer classified as sarcomas. Metastatic lesions are usually epithelial in around 70%, have both epithelial and sarcomatous component in 25% while only 5–6% are exclusively sarcoma [1].

Immunohistochemistry profiling is supportive of the presence of both the components. Mullerian origin has positive Cytokeratin (CK) 7 and CK 20 negative. Positive stain for vimentin, SMA, Desmin, focal CK shows mesenchymal component while the epithelial component shows diffuse CK staining. P53 expression typically shows a concordance between epithelial and mesenchymal components suggesting a monoclonal origin. Estrogen and progesterone receptors are variable expressed. The tumour biology of all carcinosarcomas whether originating from ovary, uterus or fallopian tube remains similar regardless of the origin. These tumours are associated with older age, obesity, nulliparity, tamoxifen usage, exogenous unopposed estrogens and exposure to pelvic radiation with a preponderance in black population [1].

Uterine carcinosarcomas (UCS) are rare and account for less than 5% of all uterine tumours. These are typically polypoidal, bulky, friable, soft and vascular tumours with areas of necrosis and haemorrhage bulging in the endometrial cavity with varying degree of myometrial extension. Ovarian carcinosarcoma (OCS) are rare tumours and account for 1–4% of all ovarian cancers. They usually present with a large tumour with massive areas of haemorrhage and necrosis. For OCS, the FIGO staging is similar to epithelial ovarian cancer (EOC) and they have a worse

K. Singh (✉)
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_22

prognosis compared to EOC. Fallopian tube carcinosarcoma are very rare and diagnosis is only made on final histopathology.

Uterine Carcinosarcoma

Case 1

Age, Parity, PS	60 years, nulliparous ECOG = 1
Presenting complaints	Post menopausal bleeding, BMI 33
Co morbidities	History of pan procto-colectomy with ileostomy for ulcerative colitis, smoker
Transvaginal sonography	Uterus bulky, endometrial thickness 30 mm with polyp, bilateral adnexa normal
Endometrial biopsy	Carcinosarcoma
MRI	1.5 cm heterogeneous mass showing areas of intermediate and high signal intensity in uterus with suspected cervical extension noted. No parametrial invasion. No enlarged pelvic or Para aortic nodes. Bilateral ovaries normal
Other investigations	CT chest: Normal CA125: 44KU/L
Surgery	Total abdominal hysterectomy with bilateral salpingo oophorectomy+ pelvic lymphadenectomy+ omental biopsy
Intraoperative findings	Extensive adhesions in the abdomen. Uterus bulky, cervix normal, growth arsing from the lower uterine segment. Bilateral ovaries were normal Rest of the pelvis and upper abdomen normal. Pelvic and paraaortic nodes not enlarged
Histology	Carcinosarcoma (malignant epithelial component 10% of tumour volume) <50% myometrial invasion, no cervical stromal involvement, parametrium normal, no LVSI, ovaries and fallopian tubes normal, omental biopsy negative Right (0/7) and left side (0/10) pelvic nodes: no evidence of malignancy; ER, PR positive FIGO stage 1A

Case 2

Age, Parity, PS	53, P3 + 0 PS = 0
Presenting complaints and examination	Irregular vaginal bleeding, foul smelling discharge × 9 months Examination: Cervix 5 cm dilated and effaced with necrotic tissues protruding through cervix. Uterus bulky
Co morbidities	BMI 44 (Wt 106 kg), previous open cholecystectomy
Histology	Carcinosarcoma from tissue removed from uterus
MRI	Heterogeneous mass predominantly in the cervix protruding into the vagina (Fig. 22.1)
Other investigations	**CT chest:** Normal
Surgery	Total abdominal hysterectomy+ bilateral salpingo oophorectomy+ bilateral pelvic lymphadenectomy + omental biopsy
Histology	Carcinosarcoma with no cervical stromal invasion. Nodes positive right side 1/8, left side 1/10

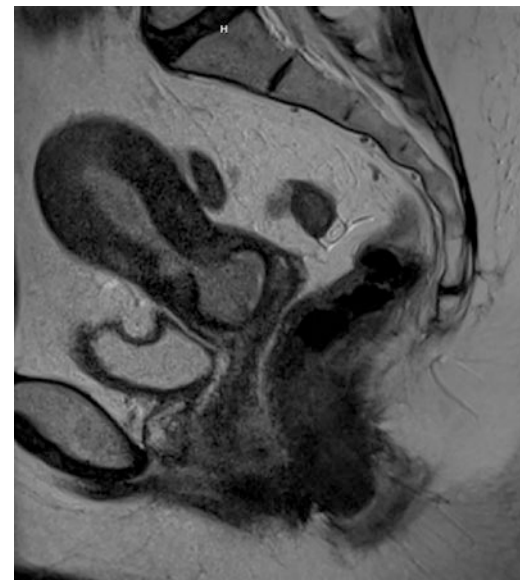


Fig. 22.1 Heterogenous mass in uterus and cervix showing areas of intermediate and high signal intensity. Cervical rim is intact

Q: What Investigations Should Be Done for this Case?

For histologically confirmed case of carcinosarcoma, investigations are directed towards assessment of tumour volume, exclude local spread and for exclusion of regional & distant metastasis. Cross-sectional imaging on MRI pelvis (gadolinium enhanced) is performed to assess uterine mass, myometrial invasion, extension to cervix, parametrium and adjacent pelvic structures and lymph nodes metastasis. MRI evaluation also helps in surgical planning to tailor the radicality of surgery required in suspected cases of stage II or above. CT chest, abdomen is done to exclude abdominal spread and distant metastasis. CA125 may be elevated in advanced stages. A baseline preoperative value may be useful during follow up post treatment, especially if initial values were elevated.

Baseline preoperative investigations including a hemoglobin, albumin levels and kidney function tests should be done for all patients.

Q: Discuss the Management Plan

The management is decided in a multi disciplinary tumour board (MDT) meeting and the pathology review should be done by an oncopathologist.

Surgery is the mainstay of treatment and complete surgical resection of the tumour with negative pathologic margins is the gold standard [2]. A thorough inspection and comprehensive evaluation of abdomen and pelvis should be done to assess extrauterine spread. In stage I, surgery includes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, omental biopsy, peritoneal biopsies and biopsy of any suspicious lesions. Complete omentectomy is not beneficial unless infiltrated with tumour deposits. For stage II disease, radical hysterectomy may be considered with cervical stromal involvement or with ballooned and enlarged cervix, in order to obtain negative margins. In advanced stages, maximum cyto reduction should be done wherever possible to achieve no residual disease which has shown a survival advantage [3]. As UCS are friable and vascular tumours, use of diathermy and vessel sealing devices may be used to minimize blood loss.

The incidence of lymph node involvement is around 14–38% in early stage in various retrospective studies and is important both for staging and prognosis.

Minimally invasive surgery (MIS) may be appropriate in early stages of carcinosarcoma cases as in any other endometrial histologies. A post hoc analysis of LAP 2 trial including type II endometrial cancer and UCS showed no difference in recurrence and survival with MIS compared to open surgery [4].

A detailed consent should be taken from the patient explaining the treatment options, stage of disease, prognosis and requirement of adjuvant therapy. The procedure and the possible complications should be explained in detail.

For this patient, due to her previous bowel surgery, additional high risk consents especially of possibility of enterotomy / bowel resection had to be taken.

Q: Role of Adjuvant Treatment in Uterine Carcinosarcomas?

Carcinosarcomas are aggressive tumours, with a high relapse rate up to 50% even in stage I. Considering the high relapse rate in early stage disease, chemotherapy is usually recommended after careful assessment by the oncologists, however, trials have not shown significant improvement in progression free survival (PFS) and overall survival (OS) with adjuvant therapies. For early stage disease, Stage IA patients can also be considered for a strict surveillance protocol and reserve adjuvant treatment for relapse. In advanced stage disease, adjuvant chemotherapy has shown improvement both in PFS and OS and is recommended.

The chemotherapy regimen usually offered is 6 cycles of Carboplatin (AUC -5) and paclitaxel (175 mg/m^2) every 21 days [2].

Role of adjuvant radiation therapy, including external beam radiotherapy and vaginal brachytherapy is not very clear. Adjuvant pelvic RT seems to be associated with better locoregional control but does not affect 5 year overall survival (OS) [5]. Prevention of local relapses

may improve quality of life, without having any effect on survival. According to some experts, external beam radiotherapy is recommended in node positive patients. RT needs to be individualized after a multidisciplinary evaluation depending upon the histopathological findings, patient performance status, toxicity profile. Combination chemoradiation as adjuvant therapy lacks validation in prospective trials [5].

Q: Management of Recurrent/ Metastatic Carcinosarcoma

Management of recurrent disease is dependent upon the site of recurrence and patient comorbidities with their performance status and response to previous treatments. Surgery, chemotherapy, radiotherapy and hormone therapy have all been used in different clinical scenarios with a therapeutic or a palliative intent. A complete assessment of loco-regional relapse and distant metastasis is usually confirmed by CT -TAP.

Surgery is usually suitable for first relapses and in cases where complete cytoreduction is feasible and where patient maintains good performance and nutritional status (albumin level > 30g/dl). In all other cases, second line chemotherapy is recommended. According to Cochrane review 2013, for stage III-IV persistent or recurrent UCS, combination chemotherapy with ifosfamide and paclitaxel was associated with significant reduction of death and disease progression compared with ifosfamide alone. However, there was significant toxicity like central nervous system toxicity, anaemia, peripheral neuropathy. Recurrent tumours which fail to respond to standard chemotherapy regimes may be biopsied as may have predominance of sarcomatous element which respond poorly to usual chemotherapy regimens. Ifosfamide combination chemotherapy is preferred in cases of sarcomatous predominance compared to carboplatin and paclitaxel with carcinomatous predominance.

Palliative radiation may be considered in cases with bleeding and bony metastasis [5].

Single agent therapy including ifosfamide, doxorubicin, carboplatin and paclitaxel have also been used to minimize toxicity in relapse cases. Trials for molecular and targeted therapy are underway.

Q: Prognosis of Uterine Carcinosarcoma

Five-year survival is around 59% with stage I disease and stage II disease, 22% for stage 3 disease while those with metastatic disease have dismal survival rates, around 10% at 5 years [1, 6].

Poor prognostic factors include age > 60 years, presence of extensive LVSI, lymph node involvement, large tumour size (>5 cm), advanced stage, deep stromal invasion, malignant peritoneal cytology, predominance of sarcoma and residual disease at surgery [7]. Heterologous component of sarcoma is associated with a poorer survival compared to homologours component [7]. Carcinoma component is most commonly observed at the metastatic site while the sarcoma component is associated with local tumor spread. Larger tumours are also a risk factor for venous thrombo embolism. Complete surgical cytoreduction is significantly associated with increased overall survival [3].

Q: What Is the Further Treatment in Case When Incidental Diagnosis Is Made Postoperatively?

In cases where there is intraoperative morcellation or supracervical hysterectomy, completion surgery is recommended for removal of cervix, pelvic +/− para-aortic nodes and other macroscopic tumour foci. In cases where the hysterectomy was total, a thorough counselling should be done and patient should be given both options of a second staging surgery followed by adjuvant treatment versus adjuvant chemotherapy +/− radiation.

Q: Explain the Follow Up Post Treatment

Follow up protocols for gynaecological cancers is constantly evolving to make it more effective and

beneficial for the patient. Self reporting of symptoms like vaginal or rectal bleeding, weight loss, pain in pelvis, abdomen, backache, cough and limb oedema, open access for medical attention improves earlier diagnosis of recurrences. Access to clinical nurse specialists and low threshold for cross sectional imaging for persistent symptoms benefits for early diagnosis of recurrences. Traditional follow up protocols are every 3–4 monthly first 2 years, then 6 monthly × 3 years.

PET/CT may be considered for cases which are being considered for secondary cytoreductive surgery as improves delineation of all suspected sites of recurrences for cytoreduction. CA125 levels may be done during follow up if they were initially elevated.

Case 1: This patient was stage Ia and after discussion at multi disciplinary meeting (MDT), she was counselled that there was lack of evidence to confirm absolute benefit of chemotherapy in early stage uterine carcinosarcomas which have been completely excised. Prognosis of carcinosarcoma is usually worse than other types of endometrial cancer. In this case chemotherapy might not be tolerated well and may be associated with increased toxicity as this patient has had a previous pan proctocolectomy, which predisposes her to dehydration and sepsis. Role of adjuvant vault brachytherapy (VBT) was also considered; however, it was disregarded as it could lead to further small bowel damage as they may be adherent to the vault. After discussion it was decided to keep her on strict surveillance and adjuvant chemotherapy and VBT would be considered if she develops relapse. The patient is on regular follow up for last 3 years.

Case 2: Adjuvant chemotherapy with pelvic radiotherapy was give in this patient as nodes were positive for malignancy

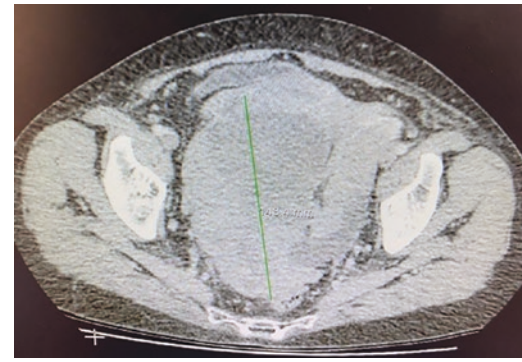


Fig. 22.2 CT scan showing heterogeneous ovarian mass with solid areas

Ovarian Carcinosarcoma

Case 3

Age, Parity, PS	78 years, P3 + 0, PS = 1, BMI = 29
Presenting complaints and examination	Bloating and abdominal distension × 6 months Large mass approximately 16 weeks arising from pelvis, ascites present
Co morbidities	Acute pulmonary embolism
CT chest abdomen and pelvis	Heterogeneous ovarian mass with solid areas, peritoneal deposits, omental cake, moderate ascites, small left upper lobe lung nodule. No enlarged pelvic or para aortic nodes (Fig. 22.2)
Other investigations	**PET CT:** Lung nodule no avid uptake **CA125:** 4573 KU/L **Serum albumin:** 30 g/dl **Image guided biopsy(IGB):** High grade serous ovarian cancer (HGSOC) **Germ line mutation analysis:** BRCA1 and BRCA 2 negative
Management	**Neoadjuvant chemotherapy:** Carboplatin +paclitaxel × 4 cycles **Post chemotherapy** CT scan: Good response, reduction in size of mass and ascites resolved Repeat CA125: 147 KU/L, serum albumin: 33 g/dl **Delayed debulking surgery: Modified posterior exenteration, supracolic omentectomy + pelvic peritonectomy + colostomy**

Intraoperative findings	Ascites 200 ml. Frozen pelvis with ovarian masses 10 × 8 cm, adherent to rectosigmoid and pouch of Douglas and pushed uterus to left side. Bladder adherent to uterus. Peritoneal infiltration with tumour in paracolic gutter and vesical peritoneum. Omentum infiltrated with tumour. Small bowel, ascending, transverse, descending colon normal. Diaphragm, spleen, liver, Morrison's pouch normal No residual disease
Histology	High grade bilateral ovarian carcinosarcoma (sarcoma grade 3) Tumour adherent to uterine serosa, rest uterus normal Metastasis in pelvic peritoneum, rectosigmoid (serosa, muscularis, pericolic adipose tissue). Omental metastasis consistent with malignant epitheial component; (CRS) 2; No involvement of fallopian tube or cervical stroma Malignant epithelial component: Positive for PAN CK, PAX-8, CK 7, WTI, aberrant P53; negative for CK20, CDX2 ER and PR Allred score 4/8 Malignant sarcomatous component: Desmin positive, S 100 patchy **FIGO stage IV A ovarian carcinosarcoma**
Adjuvant treatment	**Patient received further adjuvant chemotherapy (carboplatin + paclitaxel)**

Q: Explanation of Revision of Histological Subtype After Cytoreductive Surgery from High Grade Serous Ovarian Carcinoma (HGSOC) to Ovarian Carcinosarcoma (OCS)?

Ovarian carcinosarcoma consist of malignant epithelial and sarcomatous elements and possibly the IGB picked up the epithelial component and post surgery both sarcomatous and epithelial elements became evident.

Choice of chemotherapy in adjuvant and neoadjuvant settings is no different in HGSOC and OCS and neoadjuvant chemotherapy option is a favoured treatment approach for stage IV disease in both OCS and HGSOC. The above patient was brought to know the disadvantage in her clinical management by a revision in the diagnosis post operatively. Also, the overall prognosis is inferior in OCS compared to HGSOC.

Q: What Are the Salient Features to Raise Suspicion of Ovarian Carcinosarcoma in the Above Case?

OCS are not always accurately diagnosed preoperatively because of heterogeneous nature of histology and are usually a post operative diagnosis as in the above case. OCS are large ovarian masses and suspicion can be made intraoperatively as they are more friable, vascular, with areas of haemorrhage and necrosis. On imaging they appear solid cystic and metastatic disease to lung and liver is more frequently seen than HGSOC.

Q: What Is the Management of Ovarian Carcinosarcoma?

The management is similar to that of HGSOC. Preoperative work up requires assessment of disease load with cross sectional imaging like CT scan of the thorax, abdomen and pelvis. Preoperative tumour markers include CA125 and CEA. Image guided biopsies may not always be accurate.

Given the rarity of tumour, evidence to guide management is limited to few non randomized prospective and retrospective data. Staging is similar to epithelial ovarian cancers. Optimal cytoreduction is the mainstay of treatment [2]. These procedures may include tumour debulking, total abdominal hysterectomy, bilateral salpingo-oophorectomy, total supracolic omentectomy, pelvic and para-aortic lymph node dissection, removal of gross macroscopic disease, bowel resection, diaphragm and spleen surgery to obtain complete cytoreduction (R0 resection) [2]. Removal of bulky lymph nodes is advocated rather than systematic lymphadenectomy in advanced disease as the latter has not proven to be of benefit in randomised controlled trials [8].

In individual cases like Stage IV disease are best treated with neoadjuvant chemotherapy and pending response are considered for delayed debulking surgery.

Adjuvant chemotherapy with carboplatin – paclitaxel as three weekly/dose dense regimes has been used. Other combination used in few

studies is platinum-ifosfamide. In some publishes series, it has been shown that chemotherapy response of OCS is similar to uterine carcinosarcomas but less than that of pure serous epithelial ovarian cancer. It is suggested that response to chemotherapy is better with a predominance of epithelial component. Tumors with a higher sarcomatous component usually respond better to surgical resection.

Role of adjuvant radiotherapy in OCS remains largely unknown. Patients may be enrolled in clinical trials of targeted treatment and immunotherapy.

Follow up protocol is similar to high grade serous ovarian cancers.

Q: Prognosis of OCS

Stage of disease at presentation is the strongest prognostic factor. Complete cytoreduction with no gross residual disease (RD) has shown a survival advantage compared to >1 cm RD in a study of 50 patients of OCS. Advanced age, high grade (of the sarcomatous component), overriding of sarcomatous component more than 25%, ki 67 overexpression and p53 mutation are other poor prognostic factors [9]. Majority of OCS present as advance stage disease, most patients relapse within 1 year of treatment completion. The overall survival is 65% with stage I and 18% with stage IIIC disease [10]. The overall 5-year survival rate is significantly worse than papillary serous disease (28.2% versus 38.4%) [11].

Fallopian Tube Carcinosarcoma

Case 4

Age, Parity, PS	60 years, P1 + 0 ECOG = 1
Presenting complaints	Abdominal distension and bloating, heaviness lower abdomen History of previous hysterectomy done for heavy menstrual bleeding
Co morbidities	Nil
CECT chest + abdomen+ pelvis	15 cm heterogeneous mass solid cystic areas. Loss of fat planes with rectosigmoid. No enlarged pelvic or para aortic nodes
Other investigations	CA125: 190 KU/L, serum albumin: 33 g/dl
Surgery	Bilateral salpingo-oophorectomy, anterior resection and colostomy, supracolic omentectomy, bilateral ureterolysis and adhesiolysis (R0 resection)
Intraoperative findings	Extensive bowel and omental adhesions in the abdomen. Left sided 15 × 12 cm ovarian mass, solid cystic densely adherent to recto sigmoid and bilateral ureters, bladder and vaginal vault with capsular rupture
Histology	Unilateral carcinosarcoma of fallopian tube origin. ***Fallopian tube is embedded within the wall of the tumour in multiple sections***. No LVSI, uterus normal, cervix normal. Tumour infiltrating rectosigmoid serosa. Mesenteric nodes negative. Omentum negative Malignant epithelial component: Positive for AE1/AE3, WTI positive in glandular areas, p53 overexpressed, P16 positive in both components, negative for ER and PR, inhibin, napsin A Malignant sarcomatous component: Positive for Desmin, S100 **FIGO stage II B carcinosarcoma of fallopian tube** **Adjuvant chemotherapy**
Follow up	Three weekly carboplatin AUC 5 to 6, paclitaxel 175 mg/m^2

Q: What Is the Management and Prognosis of Fallopian Tube Carcinosarcoma?

Carcinosarcoma of the fallopian tube is extremely rare and evidence regarding the management is restricted to few case reports. Differentiation from ovarian carcinosarcoma can only be made on histology. Management is similar to that of OCS, optimal cytoreduction followed by adjuvant platinum based chemotherapy. In a review of 59 cases of fallopian tube carcinosarcomas, 3-year survival rates were 63% in stage I/II patients and 40% for stage III/IV patients [12].

Conclusion

Carcinosarcomas are highly aggressive tumours and have a malignant epithelial and sarcomatous

component. Surgery remains the mainstay of treatment. Carcinosarcomas are highly vascular tumours and caution about excessive perioperative bleeding should always be kept in mind. Adjuvant platinum based chemotherapy may show some survival benefit especially in advanced stages. Role of radiotherapy is limited.

Key Points

- Carcinosarcomas (CS) of uterine, ovary and fallopian tube have no difference in clinical outcome when compared stage to stage
- Diagnosis is confirmed by immune histochemistry; they are CK 7 positive and CK 20 negative. The mesenchymal component shows positive stain for vimentin, SMA, desmin while epithelial component shows diffuse CK staining and P53 aberrant/ positive. Estrogen and progesterone receptors are variably expressed.
- Surgery is the mainstay of treatment for all carcinosarcomas in all stages with an aim to achieve complete cytoreduction. It is also preferred for treatment of recurrent and metastatic disease
- All advanced stage carcinosarcomas are treated with neoadjuvant chemotherapy which is a combination of Carboplatin and Paclitaxel and epithelial component is more chemo sensitive
- Chemotherapy is recommended for early stage in adjuvant setting in all CS; possibly spared for stage IA uterine carcinosarcoma
- In recurrent CS, carboplatin and ifosfamide has been used
- Radiotherapy is used only in recurrent settings for palliative control of disease
- Over all prognosis is poor and similar in all CS. Five-year overall survival for stage I and stage II is 55–60%, stage III: 22% and metastatic disease is 10%

References

1. Denschlag D, Ulrich UA. Uterine carcinosarcomas - diagnosis and management. Oncol Res Treat. 2018;41(11):675–9.
2. Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, Leitao MM, Powell MA, Poveda A, Beale P, Glasspool RM, Creutzberg CL, Harter P, Kim JW, Reed NS, Ray-Coquard I. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. Int J Gynecol Cancer. 2014;24(9 Suppl 3):S55–60.
3. Tanner EJ, Leitao MM Jr, Garg K, Chi DS, Sonoda Y, Gardner GJ, Barakat RR, Jewell EL. The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma. Gynecol Oncol. 2011;123(3):548–52.
4. Fader AN, Java J, Tenney M, Ricci S, Gunderson CC, Temkin SM, et al. Impact of histology and surgical approach on survival among women with early-stage, high-grade uterine cancer: an NRG Oncology/ Gynecologic Oncology Group ancillary analysis. Gynecol Oncol. 2016;143(3):460–5.
5. Galaal K, van der Heijden E, Godfrey K, Naik R, Kucukmetin A, Bryant A, Das N, Lopes AD. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane Database Syst Rev. 2013;2013(2):CD006812.
6. Matsuo K, Johnson MS, Im DD, Ross MS, Bush SH, et al. Survival outcome of women with stage IV uterine carcinosarcoma who received neoadjuvant chemotherapy followed by surgery. J Surg Oncol. 2018;117(3):488–96.
7. Matsuzaki S, Klar M, Matsuzaki S, Roman LD, Sood AK, Matsuo K. Uterine carcinosarcoma: contemporary clinical summary, molecular updates, and future research opportunity. Gynecol Oncol. 2021;160(2):586–601.
8. Benedetti Panici P, Giannini A, Fischetti M, Lecce F, Di Donato V. Lymphadenectomy in ovarian cancer: is it still justified? Curr Oncol Rep. 2020;22(3):22.
9. Boussios S, Karathanasi A, Zakynthinakis-Kyriakou N, Tsiouris AK, Chatziantoniou AA, Kanellos FS, Tatsi K. Ovarian carcinosarcoma: current developments and future perspectives. Crit Rev Oncol Hematol. 2019;134:46–55.
10. George EM, Herzog TJ, Neugut AI, Lu YS, Burke WM, Lewin SN, Hershman DL, Wright JD. Carcinosarcoma of the ovary: natural history, patterns of treatment, and outcome. Gynecol Oncol. 2013;131(1):42–5.
11. Rauh-Hain JA, Diver EJ, Clemmer JT, Bradford LS, Clark RM, Growdon WB, Goodman AK, Boruta DM 2nd, Schorge JO, del Carmen MG. Carcinosarcoma of the ovary compared to papillary serous ovarian carcinoma: a SEER analysis. Gynecol Oncol. 2013;131(1):46–51.
12. Yokoyama Y, Yokota M, Futagami M, Mizunuma H. Carcinosarcoma of the fallopian tube: report of four cases and review of literature. Asia Pac J Clin Oncol. 2012;8(3):303–11.

Part V

Case Based Studies: Vaginal and Vulval Cancer

Malignant Diseases of Vagina

23

Bindiya Gupta and Kavita Singh

Introduction

Primary vaginal cancer is defined as tumor confined to vagina and not arising from cervix, uterine body or vulva which can be excluded by clinical examination, imaging, endometrial biopsy, colposcopy, vulvoscopy and hysteroscopy. It is a rare malignancy and accounts for less than 2% of all gynecologic malignancies [1, 2]. HPV infection (Types 16, 18, 33, 45) is associated with squamous cell cancer, the most common histologic subtype. Risk factors include advanced age (>60 years), multiple sexual partners of self or of male partner, early age at first intercourse, current smokers,previous treatment for an ano–genital tumor and Human immunodeficiency virus (HIV) infection.

In this chapter we are going to discuss various case scenarios of vaginal cancer.

Case 1: Early Stage

Age, Parity, PS	48 years, P3 + 0 ECOG = 0
Presenting complaints	Post menstrual spotting, post coital bleeding Examination: discrete lesion post fornix 1 × 2 cm just going to subvaginal tissue in fornix, cervix normal Cervical smear negative; HPV positive
Co morbidities	Nil
Biopsy (vaginal growth)	Moderately differentiated squamous cell cancer
MRI	Thickened enhancing vaginal lesion 1 × 1.5 cm in the posterior one third of vagina going in subvaginal tissue, no hydronephrosis, no pelvic lymphadenopathy No parametrial invasion. Bilateral ovaries normal
PET CT	FDG avid tumor noted in the posterior upper one third of vagina. No extra pelvic disease, no distant metastasis
Surgery	Radical hysterectomy + upper vaginectomy + bilateral pelvic lympadenectomy

Q: Etiology of Vaginal Cancer

The most common histology is squamous cell carcinoma (80–90%) followed by adenocarcinoma in 4–10% cases. Other rare histological types include malignant melanoma, neuroendocrine carcinomas and papillary squamo-transitional cell carcinomas

B. Gupta (✉)
UCMS and GTB Hospital, New Delhi, India

K. Singh
Birmingham City Hospital, Birmingham, UK
e-mail: kavitasingh@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_23

[3]. Metastatic vaginal tumors can be due to direct extension of cervical or vulvar tumors or through lymphatic or vascular metastases from endometrial cancer and gestational trophoblastic disease, respectively. Metastatic or direct extension of non-gynecologic tumors to the vagina can also occur from the urinary bladder, urethra, periurethral glands, rectum, and rarely the breast, lung, or other sites [4].

High-risk human papilloma viruses [HPV]s is associated with vaginal squamous cell cancer with a positivity rate of 66.7% (95% CI = 54.7–77.8) and common subtypes are HPV16, 18, and HPV33 [5]. Vaginal intraepithelial neoplasia (VaIN) is the precursor lesion in HPV induced squamous cell cancer and is positive in 85.2% cases with the most predominant subtypes as HPV16, followed by HPV33, and HPV45 [5].Adenocarcinoma usually develops from vaginal adenosis in women with intrauterine exposure to diethylstilbestrol, although this malignancy can also arise in patients without antenatal exposure to synthetic estrogens [6]. Other histological subtypes like clear cell carcinoma may arise from endometriosis.

Q: Clinical Presentation and Patterns of Spread of Vaginal Cancer

Symptoms are similar to cervical cancer and include vaginal bleeding, foul smelling vaginal discharge, urinary and bowel symptoms, post coital bleeding and constitutional symptoms. Clinically it appears as an ulcerating or fungating vaginal mass or an annular constricting lesion in the vagina. Squamous cell cancers tend to occur more commonly in the proximal third of vagina in the posterior wall (46%) [7]**.**

Vaginal carcinoma spreads by direct local extension to cervix, vulva, paracervical and paravagial tissues, bladder and rectum, and by lymphatic via to loco-regional nodes. The upper two-thirds of the vagina drain to obturator, hypogastric and external iliac nodes like the uterine cervix, whereas the distal third drains to the groin nodes like the vulva. The posterior vaginal wall can also drain to pre-sacral nodes via para-rectal lymphatics. Distant metastases are uncommon [8].

Q: Pre Operative Workup

The diagnosis is confirmed on histopathology. Colposcopy of the cervix and vulva should be done to exclude any lesion. Cervical smear should be done in all cases. Occasionally, examination under anesthesia may be required to assess local spread especially in post menopausal women. In cases of palpable groin lymph nodes, biopsy or fine-needle aspiration may be performed to exclude malignancy.

Magnetic resonance imaging is useful in delineating tumor size, extension toparavaginal tissue, parametrial involvement, local extension to bladder or rectum both in primary, recurrent and metastatic cancers, and can be useful in staging of disease [9]. Primary vaginal on T2-weighted images appear as intermediate or high signal intensity in contrast to the hypointense muscularis and submucosa [10]. Dynamic contrast enhancement may be also helpful in distinguishing recurrence from fibrosis and evaluating tumor extension [10]. In order to appreciate the tumor thickness and volume more accurately, a vaginal gel or a dry vaginal tampon can be instilled to distends the vaginal walls. For stage 1 disease the documented accuracy of MRI is 88–97% and the accuracy for detecting bladder and rectal invasion is 96–99% [11, 12].

PET scan helps to assess nodal metastasis and distant extrapelvic disease both in primary and recurrent disease and its sensitivity for nodal disease is greater than that of CT or MRI alone [13].

Q: Indications for Primary Surgery, Type of Surgery

Due to the anatomy of the region and the close proximity of the vagina to critical pelvic structures such as the bladder, urethra and rectum, surgery has a limited role in the management and

is indicated in Stage I disease with small lesions confined to the vaginal mucosa (less than 2 cm) [14]. Adenocarcinoma (especially clear-cell adenocarcinoma) is poorly sensitive to radiation therapy, and surgical therapy is preferred [4].

Surgery involves removal of primary disease and regional draining lymph nodes and is based on the site and range of occurrence of the primary lesion. In general terms, cancers arising in the upper third of the vagina are treated akin to cervical cancers and those arising in the lower third of the vagina are treated akin to vulval cancers. In tumors limited to upper vagina, surgery includes radical hysterectomy, or modified radical hysterectomy and pelvic lymphadenectomy, and vaginectomy with sufficient excision margin as in this case. The aim is to attain a 1 cm disease-free margin. The role of sentinel lymph nodes is still experimental.

For lower vaginal disease, radical wide local excision with 1 cm margins is recommended in addition to bilateral groin node dissection.

Pelvic exenteration may be considered in case of isolated central recurrence or even in stage IVa disease (presence of rectovaginal or vesico vaginal fistula). These patients require extensive counselling regarding the risks and morbidity of surgery, as well as the impact on quality of life and body image. Rarely palliative management of recurrent or advanced disease (Stage IV disease), a palliative urinary diversion or colostomy can be offered to improve quality of life before definitive management with radiation treatment [14, 15].

Other surgical treatments used include ovarian transposition in women before radiation therapy and laparoscopic resection of bulky nodes in advanced disease for staging.

Q: Role of Radiotherapy in the Present Case

Radiotherapy can be offered in patients who are unfit for surgery. High dose irradiation (HDR) brachytherapy alone may be considered in stage 1 vaginal cancer (tumor thickness of ≤5 mm) although it may have intrapelvic recurrences ranging from 20–30% [16]. A cylindrical or ovoid applicator may be used to conduct intracavitary irradiation or even interstitial brachytherapy is used especially if there is any doubt of submucosal invasion [17]. In Stage I tumor thickness >5 mm, external beam irradiation (EBRT) is added in combination with brachytherapy.

Q: Adjuvant Treatment

Postoperatively, if risk factors such as a positive margins or lymph node metastasis are present, radiation therapy is recommended as an adjuvant therapy [18].

Q: Prognosis

The main determinant of prognosis in carcinoma of the vagina is the stage of disease at the time of diagnosis. Squamous cell cancer has better prognosis compared to other histologic variants. Additional factors are tumor volume (>4 cm), location outside of the upper third of the vagina, HPV status, and MIB-1 index for squamous cell cancers [8, 14]. The 5 year survival is reported as 77.6% in stage 1, 52%in stage 2, 42.5% in stage 3, 20.5% in stage IVA and 12.9% in stage IV B [19].

Case 2: Advanced Stage

Age, Parity, PS	60 years, P4L4 ECOG = 1
Presenting complaints	Post menopausal bleeding, BMI 28 Examination: growth present in left vaginal fornix 2x 3 cm, extending to mid third of vagina Cervical smear negative; HPV positive
Co morbidities	Hypertension, chronic smoker

Biopsy (vaginal growth)	Moderately differentiated squamous cell cancer, p16 positive
MRI	Enlarged left obturator node, thickened vaginal lesion identified 2x3 cm going in subvaginal tissue, no hydronephrosis No parametrial invasion. Bilateral ovaries normal
PET CT	No extra pelvic disease, FDG positive left obturator node, uptake in vaginal area

Q: Further Management

The treatment of carcinoma of the vagina depends on age, performance status, tumor size, anatomical localization of the lesion and stage of the disease [2, 14]. Except for stage I, majority of cases radiation is the treatment of choice. Definitive treatment is EBRT with concurrent chemotherapy followed by brachytherapy (vaginal or interstitial) [20]. EBRT to the pelvis includes pelvic nodes and in addition, the groin nodes may be included if the tumor is in the distal vagina. It must include the area of the rectal lymphatic nodes if the tumor invades the posterior wall of the vagina, and must include the vulva if it invades the vaginal entrance. Interstitial brachytherapy (ISBT) provides a better treatment option for bulky residual disease following EBRT. Small or superficial cancers not amenable to surgical resection can be treated with ISBT alone. Where it is not feasible to treat with brachytherapy, a radical dose of radiotherapy can be delivered either with simultaneous integrated boost (SIB) or using multiple treatment phases [20].

Concurrent chemotherapy with Cisplatin can be used alongside EBRT with the data taken from the cervical cancer experience. Therapy with this combination of treatment, utilising radiotherapy doses between 70–80 Gy EQD2 appear to confer a survival advantage [14, 20].

Depending on the tumor stage, radiotherapy alone can achieve high local control rates, ranging from 85–95% for FIGO stage I, to 70–80% for FIGO stage II and around 50–70% for FIGO stages III–IVA [21].

	The patient underwent chemoradiation as the node was FDG avid. Post chemoradiation the nodal size reduced in size by 30%; but FDG avid. Thickening in left fornix Underwent total pelvic externetration with LEER due to persistent disease after chemoradiation Three years post treatment, patient is free of disease

Case 3: Rare Vaginal Tumor: Papillary Serous Cancer

Age, Parity, PS	56 years, P4L4 ECOG = 1
Presenting complaints	Growth in perineum ×4 months BMI 26 Examination: Growth present 1 × 2 cm in Para urethral region, extending to lower third of anterior vagina
Co morbidities	Nil, chronic smoker
Biopsy (vaginal growth)	High grade papillary serous vaginal cancer, p16 negative p53 aberrant
MRI	Thickened vaginal lesion in anterior vagina close to urethra. No extension in subvaginal tissue, no parametrial or paravaginal invasion. No lymphadenopathy. Bilateral ovaries normal
PET CT	No nodal or distant metastasis
Treatment	Radical wide local excision Hysterectomy + BSO

Q: Discuss Serous Cancers of Vagina

Serous carcinoma of the vagina are very rare tumours and are usually associated with advanced ovarian malignancy. Only few case reports have been reported in literature. Spread of serous cancers to vagina can occur by direct extension from a prior peritoneal site, by topical dissemination, or lymphatic and vascular spread [22].

Histopathological assessment with immunohistochemistry helps to clinch the diagnosis. CA125 may be elevated in these cases.

Since majority are metastatic a detailed assessment of the upper genital organs is mandatory and PET CT scan should be done in all cases.

In this case the margins were close (4 mm) on final histopathology. Ovaries and bilateral tubes and ovaries were negative. Further options discussed in MDT included adjuvant chemotherapy/inguinal lymphadenectomy/ radiotherapy / observation. It was further decided that patient to be kept o observation and other options to be kept in case of recurrent disease.

Case 4: Vaginal Melanoma

Age, Parity, PS	68 years, P4L4 ECOG = 1
Presenting complaints	Post menopausal spotting Excessive vaginal discharge Examination: Anterior vaginal wall 0.5 cm × 1 cm raised lesion brownish black in
Co morbidities	Diabetes type −2
Biopsy (vaginal growth)	Vaginal melanoma S-100 positive
MRI	Thickened vaginal lesion in anterior vagina. No extension in subvaginal tissue, no parametrial or paravaginal invasion. No lymphadenopathy. Bilateral ovaries normal
PET CT	No distant metastasis
Treatment	Radical wide local excision

Q: Discuss Management of Vaginal Melanoma

Malignant melanoma of vagina is a rare tumor and accounts for less than 3% of all vaginal malignancies, and for 0.3–0.8% of all malignant melanomas [23]. The clinical presentation includes complaints of vaginal bleeding, vaginal discharge or a palpable mass. The mass can be unifocal or multifocal (20%), most commonly seen in distal third of anterior vaginal wall, are usually blue-black or black-brown, while in 10% may not be pigmented (amelanotic melanoma).

Immuno -histochemical markers such as HMB-45 and S-100 can be used to confirm the diagnosis. Due to high propensity of local extension, lymphatic and hematogenous spread a distant metastasis should be ruled out. PET CT scan and Magnetic Resonance imaging (MRI) are the investigations of choice. Due to paramagnetic properties of melanin, specific signal intensity on MRI helps to distinguish melanoma from other malignancies besides accurately estimating the local extension of disease. These include a high signal intensity on T1-weighted images and low signal intensity on T2-weighted images, not suppressed by fat-saturated sequences [24].

Wide local excision is the mainstay of treatment and the aim is to completely resect the tumor with a 1–2 cm tumor free margin [25]. Total pelvic exenteration with/without adjuvant radiotherapy may be considered in patients presenting with large vaginal melanomas involving the urethra, the bladder, and/or the rectum. The removal of macroscopically involved groin and/or pelvic nodes could improve the loco-regional control of disease [25].

Radiotherapy is used as primary definitive primary treatment in patients with surgically unresectable disease or in patients who refuse surgery. It is also used for adjuvant postoperative treatment in patients with no clear surgical margins, tumor size >3 cm or positive groin or pelvic nodes [26].

Chemotherapy with platinum compounds, dacarbazine and temozolomide, either alone or in combination have not proved to be of much benefit. Immunotherapy using various multikinase inhibitors (including sorafenib), targeting placenta-derived mesenchymal stem cells is under investigation. Application of high-dose interferon-α-2b may also be an effective neoadjuvant treatment in melanoma [27].

Tumor stage, tumor size (3 cm cut off), and nodal status are the strongest predictors of clinical outcome. Vaginal melanomas are associated with high risk of recurrence, distant metastases and 5-year survival of 18–20% [25, 26].

Key Points

- Radiotherapy (usually concurrent chemoradiation) using EBRT and/or vaginal brachytherapy, is the standard therapeutic option for

primary invasive squamous cell carcinoma of the vagina

- Surgery should be reserved to accurately selected cases of stage 1, central recurrent or IVa tumours in selected patients
- Advanced stage is the strongest unfavorable risk factor and other factors include tumor size >4 cm, tumor location outside the upper third of the vagina and old age at presentation

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.
2. Adams TS, Rogers LJ, Cuello MA. Cancer of the vagina: 2021 update. Int J Gynaecol Obstet. 2021;155 Suppl 1(Suppl 1):19–27. https://doi.org/10.1002/ijgo.13867.
3. Khurana A, Gupta G, Gupta M, Kaur M. Primary neuroendocrine carcinoma of the vagina with coexistent atypical vaginal adenosis: a rare entity. J Cancer Res Ther. 2013;9(2):328–30.
4. Hacker NF, Eifel PJ, van der Velden J. Cancer of the vagina. Int J Gynaecol Obstet. 2012;119(Suppl 2):S97–9.
5. Bertoli HK, Rasmussen CL, Sand FL, Albieri V, Norrild B, Verdoodt F, Kjaer SK. Human papillomavirus and p16 in squamous cell carcinoma and intraepithelial neoplasia of the vagina. Int J Cancer. 2019;145(1):78–86.
6. Conlon JL. Diethylstilbestrol: Potential health risks for women exposed in utero and their offspring. JAAPA. 2017;30(2):49–52.
7. Slomovitz BM, Coleman RL. Invasive cancer of the vagina. In: DiSaia PJ, Creasman WT, editors. Clinical gynecologic oncology, vol. 8. Philadelphia: Elsevier Saunders; 2012. p. 245–59.
8. Gadducci A, Fabrini MG, Lanfredini N, Sergiampietri C. Squamous cell carcinoma of the vagina: natural history, treatment modalities and prognostic factors. Crit Rev Oncol Hematol. 2015;93(3):211–24.
9. Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol. 2003;91(1):59–66.
10. Gardner CS, Sunil J, Klopp AH, et al. Primary vaginal cancer: role of MRI in diagnosis, staging and treatment. Br J Radiol. 2015;88(1052):20150033.
11. Donati OF, Lakhman Y, Sala E, Burger IA, Vargas HA, Goldman DA, Andikyan V, Park KJ, Chi DS, Hricak H. Role of preoperative MR imaging in the evaluation of patients with persistent or recurrent gynaecological malignancies before pelvic exenteration. Eur Radiol. 2013;23(10):2906–15.
12. Kim WY, Chang SJ, Chang KH, Yoo SC, Lee EJ, Ryu HS. Reliability of magnetic resonance imaging for bladder or rectum invasion in cervical cancer. J Reprod Med. 2011;56(11-12):485–90.
13. Robertson NL, Hricak H, Sonoda Y, Sosa RE, Benz M, Lyons G, Abu-Rustum NR, Sala E, Vargas HA. The impact of FDG-PET/CT in the management of patients with vulvar and vaginal cancer. Gynecol Oncol. 2016;140(3):420–4.
14. Adams TS, Cuello MA. Cancer of the vagina. Int J Gynaecol Obstet. 2018;143(Suppl 2):14–21.
15. Saito T, Tabata T, Ikushima H, Yanai H, Tashiro H, Niikura H, et al. Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of vulvar cancer and vaginal cancer. Int J Clin Oncol. 2018;23(2):201–34.
16. Frank SJ, Jhingran A, Levenback C. Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiat Oncol Biol Phys. 2005;62:138–47.
17. Vargo JA, Kim H, Houser CJ, Sukumvanich P, Olawaiye AB, Kelley JL, Edwards RP, Comerci JT, Huang M, Courtney-Brooks M, Beriwal S. Image-based multichannel vaginal cylinder brachytherapy for vaginal cancer. Brachytherapy. 2015;14(1):9–15.
18. Rajaram S, Gupta B. Malignant diseases of vagina. In: Gandhi A, Tank P, Purandare A, editors. FOGSI's post graduate gynaecology, vol. 2. Jaypee; 2021.
19. Hacker NF. Vaginal cancers. In: ESGO textbook of gynaecological oncology. 4th ed. Ed Publishers. p. 984–8.
20. Allos B, Fernando IN, Walji N. Radiation protocols relevant to gynaecological oncology and management of complications. In: Singh K, Gupta B, editors. Gynaecological oncology: basic principles and clinical practice. Cham: Springer; 2022.
21. Schnürch HG, Ackermann S, Alt-Radtke CD, Angleitner L, Barinoff J, Beckmann MW, et al. Diagnosis, therapy and follow-up of vaginal cancer and its precursors. Guideline of the DGGG and the DKG (S2k-Level, AWMF Registry No. 032/042, October 2018). Geburtshilfe Frauenheilkd. 2019;79(10):1060–78.
22. Kadour-Peero E, Sagi-Dain L, Cohen G, Korobochka R, Agbarya A, Bejar J, Sagi S. Primary papillary serous carcinoma of the fallopian tube presenting as a vaginal mass: a case report and review of the literature. Am J Case Rep. 2018;19:534–9.
23. Gökaslan H, Sişmanoğlu A, Pekin T, Kaya H, Ceyhan N. Primary malignant melanoma of the vagina: a case report and review of the current treatment options. Eur J Obstet Gynecol Reprod Biol. 2005;121(2):243–8.
24. Sugiyama VE, Chan JK, Kapp DS. Management of melanomas of the female genital tract. Curr Opin Oncol. 2008;20(5):565–9.

25. Gadducci A, Carinelli S, Guerrieri ME, Aletti GD. Melanoma of the lower genital tract: prognostic factors and treatment modalities. Gynecol Oncol. 2018;150(1):180–9.
26. Kirschner AN, Kidd EA, Dewees T, Perkins SM. Treatment approach and outcomes of vaginal melanoma. Int J Gynecol Cancer. 2013;23(8):1484–9.
27. Terzakis E, Androutsopoulos G, Adonakis G, Zygouris D, Grigoriadis C, Decavalas G. Vaginal primary malignant melanoma: report of four cases and review of the literature. Eur J Gynaecol Oncol. 2011;32(1):122–4.

24 Vulval Squamous Cell Cancer: Preneoplastic Conditions, Early Stage, Advanced Stage

Audrey Kwong and Jason Yap

Introduction

Vulval cancer constitutes around 6% of all gynaecological malignancies and the incidence increases with age. It also affects women from poorer sociodemographic backgrounds. VSCC accounts for 90% of all cases of vulval cancer.

Women will usually present with a tender vulval lesion and/or symptoms such as persistent itching which does not improve with topical medications. Fifty percent of cases of VSCC arise from the labia majora while 2 in 10 involve the labia minora [1]. Other sites include the clitoris and Bartholin's gland. Some patients may report symptoms such as urine retention or poor micturition as a consequence of urethral outflow obstruction. If the tumour invades into the anal sphincters or rectum, this can result in faecal incontinence or anovaginal fistulas. Unfortunately, the diagnosis is often delayed by up to a year in some cases as women are often too embarrassed to seek medical attention [2]. VSCC may arise through two common pathways: Human papillomavirus (HPV)-dependent and HPV-independent as illustrated in Table 24.1. These two pathways may not be mutually exclusive as previously assumed, as histological examination reveals that lichen sclerosis (LS), usual type Vulval Intraepithelial Neoplasia (uVIN) and differentiated VIN (dVIN) may coexist in a third of cases of VSCC [3].

This chapter will discuss various case scenarios of vulval squamous cell cancer and their management which often depend on the patient's age, performance status, and co-morbidities and the disease stage.

A. Kwong · J. Yap (✉)
PanBirmingham Gynaecological Cancer Centre, City Hospital, Birmingham, UK

Institute of Cancer and Genomic Sciences, College of Dental and Medical School, University of Birmingham, Birmingham, UK
e-mail: jason.yap@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_24

Table 24.1 Differences between HPV-dependent and HPV-independent VSCC

	HPV-dependent	HPV-independent
Age at presentation	Under 65 years	65 years and above
Proportion of VSCC	40%	60%
Mechanism	Persistent infection with high-risk HPV strains including HPV 16, 18 and 33 induce oncogenic transformations	Chronic inflammation leads to DNA damage and p53 mutations following sustained epithelial cell renewal and repair
Precursor lesion	uVIN	dVIN, possibly LS
Type of VSCC	Basaloid or warty-type	Keratinising

Case 1: Squamous Cell Cancer Vulva: Early Stage

Age, PS	56 years, P1+0, WHO Performance Status 1
Clinical presentation	Progressively worsening vulval irritation and pain for over 2 years associated with a 5 × 6 cm ulceroproliferative lesion over the clitoris. No palpable inguinofemoral lymph nodes
Co-morbidities	Nil
Biopsy	Poorly differentiated vulval squamous cell carcinoma (VSCC)
Pre-operative CT abdomen and pelvis	No evidence of regional or distant metastasis
Surgery	Radical anterior vulvectomy and bilateral pudendal thigh flaps reconstruction (Fig. 24.1), and bilateral inguinofemoral lymphadenectomies
Histology	SCC, margins are clear of cancer. Positive inguinofemoral lymph nodes bilaterally with extracapsular spread. FIGO stage IIIC
Adjuvant treatment	Adjuvant radiotherapy to both groins and pelvic sidewall

Q: What Investigations Are Recommended in Women Diagnosed with VSCC?

Examination

A meticulous examination of the urethra, lower genital tract and anus should be conducted to assess for premalignant lesions such as vulval, vaginal, cervical and anal intraepithelial neoplasia or other synchronous cancerous lesions. The groin nodes should be palpated to determine whether lymphadenopathy is present.

Biopsy

A tissue biopsy is essential and may usually be procured via a Keyes punch biopsy. The biopsy specimen should be full-thickness and include the interface between the tumour and healthy adjacent tissue [3]. Excision biopsies should be avoided and sampling ulcerated or necrotic areas should be averted as these are likely to yield inconclusive histology results.

Imaging

Cross-sectional imaging such as MRI and CT scans are of limited benefit as they lack the sensitivity and specificity to detect nodal micrometastases and will therefore yield false negative results in women without palpable lymph nodes [4]. However, all women with a large tumour (typically >4 cm) and clinically enlarged inguinal lymph nodes should undergo a staging CT scan (thorax, abdomen and pelvis) to evaluate for distant metastasis.

Q: What Is the Management of Patients with Early and Locally Advanced Stage VSCC?

All cases should be discussed at the regional MDT meeting. Surgical excision remains the cornerstone of treatment for women with early stage VSCC. The objective of surgery is to obtain additional informa-

tion for staging purposes (diagnostic) and to alleviate patient symptoms (therapeutic).

The extent of surgery will depend on patient and tumour factors.

- ***Patient factors:*** women with VSCC are generally older and usually suffer from multiple comorbidities. Their performance status and individual wishes should thus be considered when contemplating surgery.
- ***Tumour factors:*** the size of the tumour, its location and proximity to vital organs such as the urethra, bladder, anal sphincters and rectum should be considered.

The aim of surgery is to achieve tumour-free margins to reduce the risk of recurrence.

In cases of large tumours with deep invasion, the depth of excision to the inferior fascia of the urogenital diaphragm, median perineal fascia or periosteum of pubic bone and, occasionally, amputation of the distal centimetre of the urethra need to be considered. This may not be required for smaller tumours [5]. Large defects may necessitate cutaneous or myocutaneous flap reconstruction [6] (Fig. 24.1). Historically, a 20 mm disease-free tissue margin was recommended to achieve a pathological margin of at least 8 mm after specimen fixation. However, recent studies have demon-

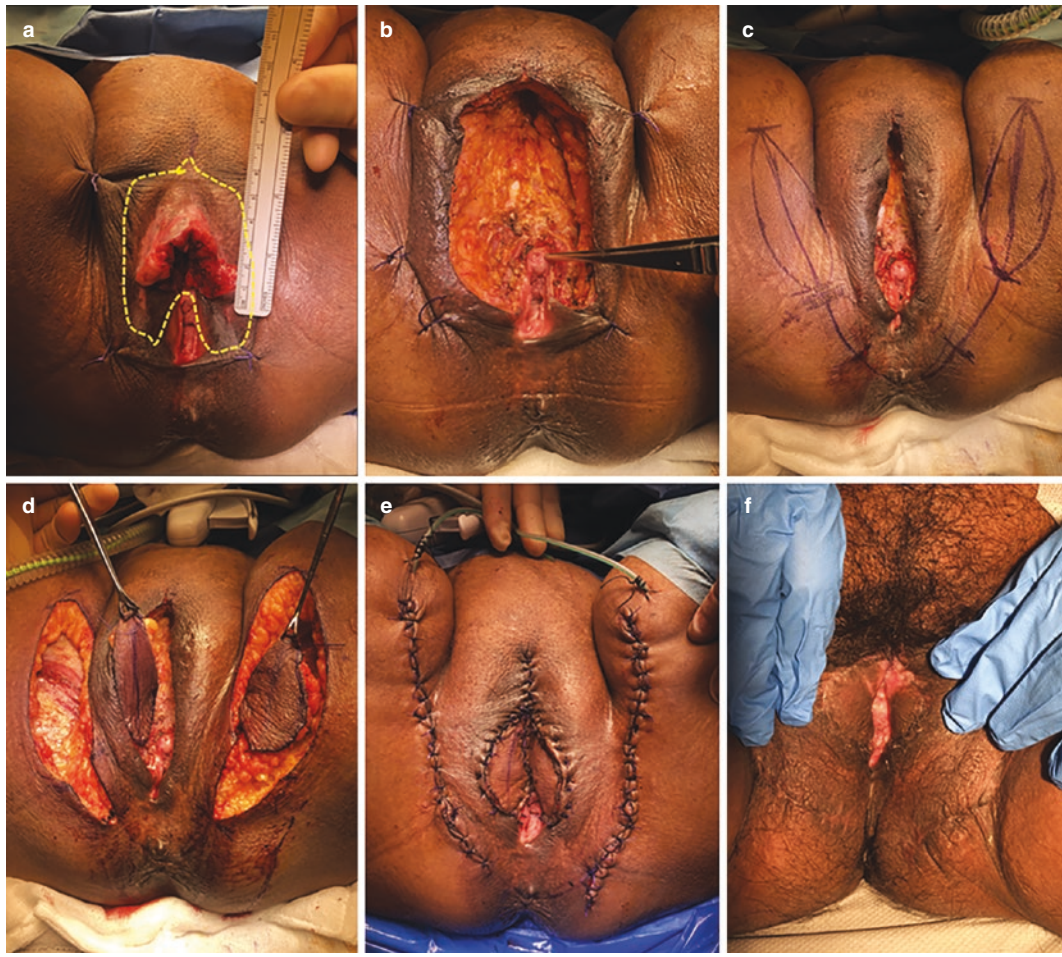


Fig. 24.1 Radical anterior vulvectomy with bilateral pudendal thigh flaps reconstruction, (**a**) squamous cell cancer involving the anterior vulva and invading the clitoris; (**b**) radical anterior vulvectomy with preservation of urethra meatus, (**c**) mapping and planning of pudendal thigh flaps reconstruction, (**d**) harvesting of fasciocutaneous skin flaps, (**e**) post-reconstruction, (**f**) 3 months after reconstruction

strated that the disease free margin has no statistically significant impact on local recurrence rates [7, 8]. Recent evidence further showed that more conservative excisions have the advantage of preserving functional and cosmetic outcomes without compromising disease free and overall survival [9]. Therefore, overzealous excisions to achieve clear margins, especially when these are likely to compromise the patient's quality of life, should be discouraged.

Where the margins are clear of disease, clinical surveillance is sufficient, a re-excision or irradiation e.g., where further surgery is not feasible or where it would inevitably impact on functional outcomes are recommended when the margins are close (≤1 mm tumour-free margin) or positive for invasion.

Locally Advanced VSCC

In cases where VSCC involves adjacent structures such as the upper vagina, bladder or anus, an exenteration may be required. This is a highly morbid procedure and should be reserved in cases where distant metastasis beyond the inguinal lymph nodes has been excluded on a PET-CT as the presence of distant metastases is associated with a poorer prognosis.

Q: What Is the Difference Between a Lateral and Central Tumour?

The tumour is considered to be lateral if its medial border is over 1 cm from the midline that is an imaginary vertical line from the clitoris to anus. These tumours are usually located over the labia majora. Any non-lateral tumour is classed as a central tumour [10].

Q: When Is Nodal Staging Required?

The decision to undertake a nodal assessment will be guided by tumour characteristics such as its subtype, laterality, dimensions and depth of invasion. Inguinofemoral lymphadenectomy serves two purposes: (1) to stage cancer and detect nodal metastasis, and (2) therapeutic if nodal metastasis [11].

Lymph node assessment is required for tumours ≥2 cm in width or with a depth of invasion (DOI) over 1 mm as the incidence of lymph node metastasis in these cases is >8% [12]. The risk of groin nodes metastasis is negligible (<1%) in cases of smaller tumours [10]. The decision to perform an ipsilateral or bilateral groin assessment depends on the location of the tumour. Lymphatics from the vulva tend to drain to the ipsilateral inguinofemoral nodal basin. For lateral tumours, an ipsilateral lymph node staging is recommended as the risk of metastatic spread to the contralateral groin is low. However, there is extensive crossover of the lymphatic system and it therefore follows that central tumours may metastasize to either the left or right groin or both. A bilateral nodal assessment is therefore required for central tumours. Similarly, a bilateral lymphadenectomy is recommended for multifocal disease as the course of lymphatic drainage is inconsistent for those tumours.

When the ipsilateral groin nodes are negative for metastasis, the risk of contralateral positivity is <3%. However, when the ipsilateral nodes are positive, a contralateral lymphadenectomy is recommended [13].

Q: Who Is a Candidate for Sentinel Lymph Node Biopsy (SLNB)?

Traditionally, total lymphadenectomy was the default operation to stage vulval cancers. This involved the removal of all superficial and deep inguinofemoral nodes within the femoral triangle. Cloquet's or Rosenmüller's lymph node has a high incidence of harboring cancer metastasis and should always be removed [11]. Attempt should be made to preserve the long-saphenous

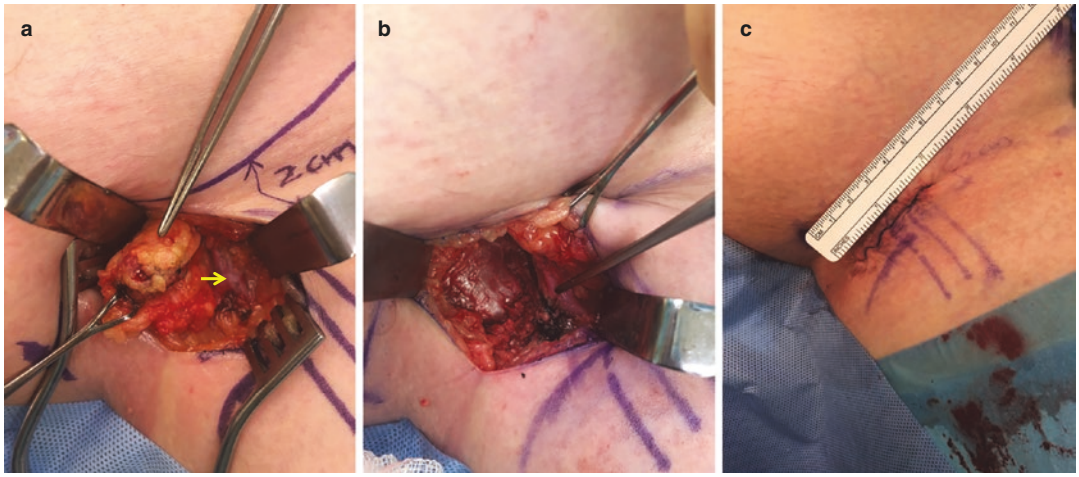


Fig. 24.2 Left inguinofemoral sentinel lymph node biopsy, (**a**) sentinel lymph node isolated medial to left saphenous vein (yellow arrow); (**b**) sentinel lymph node excised over iliopectineus muscle. The saphenous vein is indicated by the Debakey forceps; (**c**) the 4 cm incision is finally closed with subcutaneous sutures

vein as this reduces the risk of post-operative leg lymphedema [11]. However, total inguinofemoral lymphadenectomy has gradually been superseded by SLNB in a select group of patients in view of the proven oncological safety and lower morbidity associated with this technique [10, 14]. In cases where the SLN cannot be detected or in cases where the SLN is positive for macrometastases (>2 mm), an inguinofemoral lymphadenectomy is recommended (see later) [5]. If ipsilateral SLN is positive, the contralateral groin should be evaluated surgically and the patient should receive adjuvant radiotherapy. If available, frozen section of sentinel node may guide the intraoperative decision making (Fig. 24.2).

Inclusion criteria for SLNB [10]

- Unifocal tumour ≤4 cm
- Stromal invasion>1 mm
- No clinical or radiological evidence of lymphadenopathy

Exclusion criteria for SLNB

- Locally advanced disease e.g., vaginal involvement
- Multifocal disease

Radio-labelled technetium-99 (Tc-99 m), in combination with blue dye (1% Isosulfan Blue) is used in the detection of SLN. However, radiocolloid used alone has gained precedence in view of the low specificity of blue dye and flooding which obscures the surgical field. These are usually injected peritumorally in four quadrants (typically at 12, 3, 6 and 9 o'clock position immediately adjacent to the tumour) and a preoperative lymphoscintigraphy may be performed to aid in identifying the number and location of the SLN(s). Intraoperatively, a gamma probe is used to localise the SLNs. The management of groin nodes in early stages is summarized in Fig. 24.3.

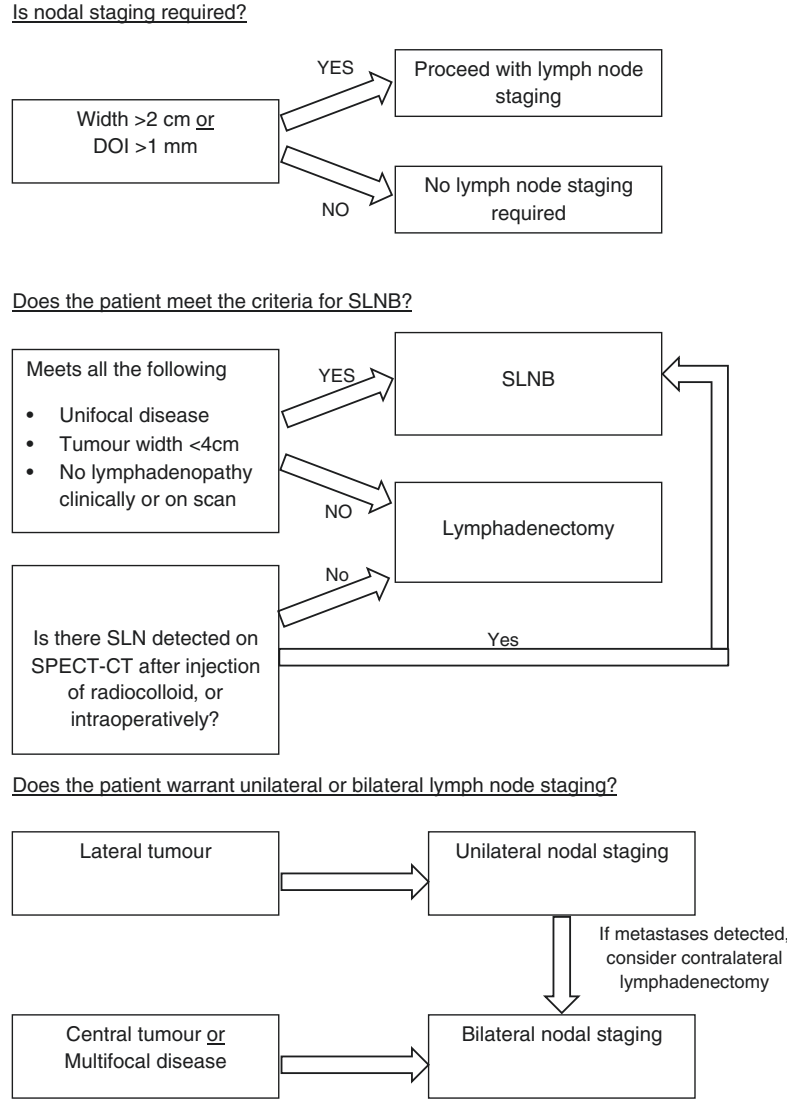


Fig. 24.3 Flowchart for patient selection for lymph node staging, SLN criteria and laterality of lymph node surgery

Q: Describe the Management of Positive Groin Nodes

Postoperative radiotherapy is warranted to reduce the risk of recurrence following inguinofemoral lymphadenectomy if groin nodes are positive for metastases [15]. Patients with two or more positive nodes or with extracapsular extension of nodal metastasis should receive pelvic and groin irradiation [16].

All patients who have a positive sentinel lymph node (one or more positive nodes), besides undergoing a full inguinofemoral lymph node dissection, should receive radiotherapy to the groins and pelvis if indicated. GROINSS-V-II, a prospective multicenter phase-II single-arm treatment trial compared the role of complete inguinofemoral lymphadenectomy versus adjuvant radiotherapy in women with positive sentinel lymph nodes [17]. The trial concluded that inguinofemoral radiotherapy is a safe and less morbid alternative for inguinofemoral lymphadenectomy in patients with SLN micrometastases (≤2 mm) with a groin recurrence rate was 1.6%. For macrometastasis (>2 mm), radiotherapy alone with a total dose of 50 Gy

resulted in a higher incidence of isolated groin recurrences compared to inguinofemoral lymphadenectomy. The authors concluded that a combination of groin lymphadenectomy and adjuvant radiotherapy offered superior survival benefit compared to radiotherapy alone and should therefore be advocated in women with macrometastasis.

What Is the Role of Radiotherapy and/or Chemotherapy in VSCC?

Radiotherapy may be considered as treatment modality in primary, neoadjuvant, adjuvant or palliative settings, with or without chemotherapy for women with VSCC.

The whole vulva, bilateral inguinal nodal chains and pelvic lymph nodes up to the level of the common iliac vessels bifurcating should be treated. A recommended dose of 45–50 Gy in 25 fractions over 5 weeks is given [18]. Concurrent weekly cisplatin may be added. Patients with WHO PS 0 and1 and adequate renal function are commonly treated with concurrent weekly cisplatin; alternative options include treatment with cisplatin and fluorouracil (5-FU) or mitomycin C and 5-FU.

Primary

Primary radiotherapy is an alternative to surgery to preserve functional outcomes in cases where the tumour invades into or is located in close proximity to vital structures such as the anal sphincters, rectum or urethra. To ensure adequate tumor coverage, clinical examination, imaging findings (CT or MRI), and nodal size should be considered to properly define the target volume during 3D planning. Patients with inoperable disease receiving external beam radiotherapy (EBRT) as the definitive treatment require a higher treatment dose to the primary tumour and involved lymph nodes. Increasingly, this is delivered with intensity modulated radiotherapy (IMRT) using the simultaneous integrated boost (SIB) approach whereby potential areas of microscopic disease receive 45 Gy in 25 fractions and areas of macroscopic disease receiving a dose of 60 Gy in 25 fractions. Good response rates are garnered from EBRT often with both complete clinical and pathological responses seen.

Primary combined chemoradiotherapy (CCRT) improves relapse-free and overall survival for the definitive treatment of vulval cancers [18]. However, radiotherapy can lead to long term radiation dermatitis, cystitis and colitis which may impact on the patient's quality of life.

Neoadjuvant

Neoadjuvant chemoradiotherapy is delivered to reduce the tumour size prior to surgery. Weekly cisplatin is recommended in view of its radiosensitising properties [3]. However, radiotherapy induced dermatitis, particularly to adjacent normal skin, can delay wound healing after surgery and may hamper the ability to harvest local skin flaps for reconstruction.

Adjuvant

Adjuvant radiotherapy may also be given when the margins are involved and in cases where further resection is not feasible.

Palliative

Radiotherapy may be useful for symptom control in inoperable unresectable tumours.

Q: Briefly Describe the Treatment of Advanced Vulval Cancer?

Advanced vulvar cancer includes metastasis extending beyond the vulva, and/or where the presence of bulky groin nodes [16].

Management of the Primary Tumour

Surgical excision of the primary tumor with clear surgical margins is the standard of care. In cases where an exenteration is considered, patients should be appropriately counselled and all cases discussed at the sMDT. Surgery may also be undertaken following neoadjuvant chemoradiotherapy after adequate diminution of the tumour size to facilitate its excision without compromising on functional status. Plastic flap reconstruc-

tion may be considered following surgical resection to restore cosmesis and function.

Management of Groin Nodes

Cross-sectional imaging such as a CT scan of the chest, abdomen and pelvis and/or PET CT should be performed to assess for metastasis to the regional and pelvic nodes, or beyond [19]. Bilateral inguinofemoral lymphadenectomies are undertaken to remove the enlarged lymph nodes along with the underlying lymphatic basin within the limit of the femoral triangles. Adjuvant radiotherapy to the groin and pelvic sidewall should be administered if inguinofemoral nodal metastasis is confirmed histologically [20].

In cases where surgery is no longer possible or when the groin nodes are ulcerated or fixe, primary radiotherapy, with or without chemo-sensitisation is recommended. A palliative resection of the inguinofemoral nodes may subsequently be considered in suitable cases. Alternatively, neoadjuvant chemotherapy with cisplatin or carboplatin and paclitaxel can be used to reduce the nodal volume prior to radiotherapy as any tumour over 2 cm is unlikely to be radio-responsive [21]. Inguinofemoral lymphadenectomy may also be considered following neo-adjuvant chemotherapy.

Q: Follow Up After Treatment?

Patients are usually followed up to monitor for any signs or symptoms of recurrence. At each visit, symptom review and a thorough clinical examination should be undertaken. Cross-sectional imaging may be considered in cases where disease recurrence is suspected [21]. Women with background lichen sclerosus are at increased risk of recurrence and should therefore remain under closer surveillance [4]. Approximately a third of patients who underwent curative treatment previously will develop local disease recurrence [4, 6]. The overall 5-year survival in women without inguinofemoral nodal involvement is excellent but this falls drastically in those with inguinofemoral nodal metastasis [22].

Case 2: Recurrent Vulval Cancer

Age, PS	69 years, P2+0, WHO Performance Status 1
Clinical presentation	New vulval lesion associated with 2 month history of itching Background: FIGO stage 1b VSCC. Previous radical wide local excision of right labium majus and ipsilateral sentinel lymph node biopsy two years previously. Histopathology results showed grade 2 VSCC arising on a background of lichen sclerosus. There was no lymph vascular space invasion and the ipsilateral SLN was negative for metastasis Examination: 2 × 3 cm tumour over left labium minus. No palpable inguinofemoral lymph nodes
Co morbidities	Coronary artery disease. Angioplasty 7 years ago
Biopsy	Well differentiated VSCC
Pre-operative CT abdomen and pelvis	No evidence of regional or distant metastasis

Q: How Are Patients with a Confirmed Recurrence of VSCC Managed?

The 5-year risk of recurrence is approximately 30%. Treatment options depend on the site(s) of the recurrence, performance status, previous treatment(s) and the findings of re-staging investigations [19].

Surgical excision of the main tumour remains the standard approach if complete resection is feasible. If the DOI exceeds 1 mm or the tumour width is over 2 cm, further nodal staging in the form of SLNB (if not done previously) or inguinofemoral lymphadenectomy should be undertaken. This patient underwent a bilateral inguinofemoral lymphadenectomy as the new lesion was within 1 cm of the midline (central tumour) and was wider than 2 cm. Adjuvant treatment is similar to that described for primary disease.

For inguinofemoral nodal recurrence, surgical resection should be considered if the disease is confined to the regional lymphatics. Systemic therapy and radiation should be considered as first line treatment if metastasis is identified in the pelvic lymph nodes and beyond on cross-

sectional imaging. However, resection of enlarged and bulky inguinofemoral lymph node measuring over 2 cm should be considered as these lymph nodes are less likely to respond to chemotherapy and radiation treatment.Alternatively, neoajuvant chemotherapy may be administered to reduce the tumour volume and facilitate surgical resection. Radiotherapy should only considered in patients who are radiotherapy naive.

Targeted therapy have been explored in vulval cancer in a phase 2 study; erlotinib, an EGFR inhibitor was associated with a clinical benefit rate of 67% in women with metastatic vulvar cancer [23]. Unfortunately, clinical trials exploring the role of systemic therapies in the treatment of vulval cancer remain limited owing to the low incidence of this condition.

Key Points

1. VSCC may arise through two common pathways: Human papillomavirus (HPV)-dependent and HPV-independent. The former is seen in a relatively younger age group, and is associated with usual type Vulval Intraepithelial Neoplasia (uVIN) while the latter is seen more often in older females in whom differentiated VIN (dVIN) may coexist in a third of cases of VSCC.
2. Surgery is the mainstay of treatment. Radical wide local excision or partial vulvectomy is recommended.
3. The aim of surgical resection is to excise the primary tumour and achieve disease free margins (typically >1 mm in all dimensions).
4. A re excision, or irradiation in cases where a further surgery is not feasible, are recommended when the margins are positive for metastasis.
5. Plastic reconstruction should be considered following surgery to restore cosmesis and functions.
6. The tumour is considered to be lateral if its medial border is over 1 cm from the midline.
7. Lymph node assessment is required in cases where tumours measure over 2 cm wide or where the depth of invasion is 1 mm or more.
8. Inclusion criteria for SLNB includes unifocal tumour measuring up to 4 cm, stromal invasion>1 mm and no clinical or radiological evidence of lymphadenopathy.
9. Radiotherapy can be given both in primary and adjuvant settings

References

1. Serrado M, Horta M, Cunha T. State of the art in vulvar cancer imaging. Radiol Bras. 2019;52(5):316–24.
2. Yap J, Baker L, Balega J, Chan K, Luesley D. Impact of improving outcome guidance in gynaecological cancer on squamous cell carcinoma of the vulva in the west midlands, UK. J Obstet Gynaecol. 2011;31(8):754–8.
3. Morrison J, Buckley L, Baldwin P, Cogswell L, Edey K, Faruqi A, et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2020;252:502–25. https://www.bgcs.org.uk/wp-content/uploads/2021/07/BGCS-vulval-guidelines-v22.pdf
4. Yap J, Fox R, Leonard S, Ganesan R, Kehoe S, Dawson C, et al. Adjacent lichen sclerosis predicts local recurrence and second field tumour in women with vulvar squamous cell carcinoma. Gynecol Oncol. 2016;142(3):420–6.
5. NCCN Clinical Practice Guidelines in Oncology. Vulval cancer. Version 1.2023- Dec 22, 2022. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf.
6. Francis JA, Eiriksson L, Dean E, et al. No. 370-management of squamous cell cancer of the vulva. J Obstet Gynaecol Can. 2019;41(1):89–101.
7. Woelber L, Griebel L, Eulenburg C, Sehouli J, Jueckstock J, Hilpert F, et al. Role of tumour-free margin distance for loco-regional control in vulvar cancer-a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. Eur J Cancer. 2016;69:180–8.
8. National Cancer Guidance Steering Group. Improving outcomes in gynaecological cancers - the manual. London: NHS Executive, Department of Health; 1999. (Guidance on commissioning cancer services - improving the outcomes).
9. Yap J, O'Neill D, Nagenthiran S, Dawson C, Luesley D. Current insights into the aetiology, pathobiology, and managementof local disease recurrence

in squamous cell carcinoma of the vulva. BJOG. 2017;124:946–54.
10. Oonk M, van Hemel B, Hollema H, de Hullu J, Ansink A, Vergote I, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol. 2010;11(7):646–52.
11. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. https://www.bgcs.org.uk/wp-content/uploads/2021/07/BGCS-vulval-guidelines-v22.pdf.
12. Gonzalez-Bosquet J, Magrina JF, Magtibay PM, et al. Patterns of inguinal groin node metastases in squamous cell carcinoma of the vulva. Gynecol Oncol. 2007;105:742–6.
13. Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. Gynecol Oncol. 2018;148(3):622–31.
14. Rajaram S, Gupta B. Management of vulvar cancer. Rev Recent Clin Trials. 2015;10(4):282–8.
15. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol. 2009;114:537–46.
16. Hacker NF, Eifel PJ, van der Velden J. Cancer of the vulva. Int J Gynecol Obstet. 2015;131(Suppl 2):S76–83.
17. Oonk MHM, Slomovitz B, Baldwin PJW, van Doorn HC, van der Velden J, de Hullu JA, et al. Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: results of GROINSS-V II. J Clin Oncol. 2021;39(32):3623–32.
18. Allos B, Fernando IN, Walji N. Radiation protocols relevant to gynaecological oncology and management of complications. In: Singh K, Gupta B, editors. Gynaecological oncology: basic principles and clinical practice. Cham: Springer; 2022.
19. Viswanathan C, Kirschner K, Truong M, Balachandran A, Devine C, Bhosale P. Multimodality imaging of vulvar cancer: staging, therapeutic response, and complications. AJR Am J Roentgenol. 2013;200:1387–400.
20. Olawaiye AB, Cuello MA, Rogers LJ. Cancer of the vulva: 2021 update. Int J Gynaecol Obstet. 2021;155 Suppl 1(Suppl 1):7–18.
21. Amant F, Nooij L, Annibali D, et al. Brief report on 3-weekly paclitaxel carboplatin efficacy in locally advanced or metastatic squamous vulvar cancer. Gynecol Obstet Investig. 2018;83:620–6.
22. Survival of vulval cancer. https://www.cancerresearchuk.org/about-cancer/vulval-cancer/survival. Accessed 23 Jan 2023.
23. Horowitz NS, Olawaiye AB, Borger DR, et al. Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol. 2012;127:141–6.

25 Vulval Cancer with Rare Histology Subtypes

Audrey Kwong and Jason Yap

Introduction

Besides squamous cell cancer, other histologies like verrucous carcinoma, melanoma, bartholin gland cancer, basal cell cancer etc. constitute 5% of all vulval cancers. The management of these rare histologies also have undergone a paradigm change to less radical surgeries and sentinel lymph node assessment to reduce wound complications and lymphedema as highlighted in the cases discussed in the chapter.

Case 1: Verrucous Tumours

Age, PS	79 years, P0 + 1, ECOG −2
Clinical presentation	Mass in perineal region associated with pain, itch and discomfort on walking. Initially presented as a small genital wart but had progressively increased in size over the last 8 months Examination: 12 cm exophytic fungating tumour over the left labia, right labia and perianal region. The mass did not infiltrate into the urethra, vagina, anal sphincters or rectum (Fig. 25.1)
Co morbidities	Nil
PET CT	No evidence of extravulval disease
Surgery	Radical vulvectomy, and VY plastic flap reconstruction
Histology	Grade 1 verrucous squamous cell carcinoma, margins were all clear of microscopic disease

Q: What Are the Signs and Symptoms of a Verrucous Carcinoma?

Verrucous carcinomas make up less than 1% of all cases of vulval cancer [1]. They are a well-differentiated form of squamous cell carcinoma (SCC). Most cases are unrelated to the human papilloma virus (HPV) [2].

Most women typically report symptoms such as pain and itch over the genital area. The tumour may reach monumental dimensions and inguino-femoral lymph nodes may also be palpable.

A. Kwong
PanBirmingham Gynaecological Cancer Centre, City Hospital, Birmingham, UK

J. Yap (✉)
PanBirmingham Gynaecological Cancer Centre, City Hospital, Birmingham, UK

Institute of Cancer and Genomic Sciences, College of Dental and Medical School, University of Birmingham, Birmingham, UK
e-mail: jason.yap@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_25

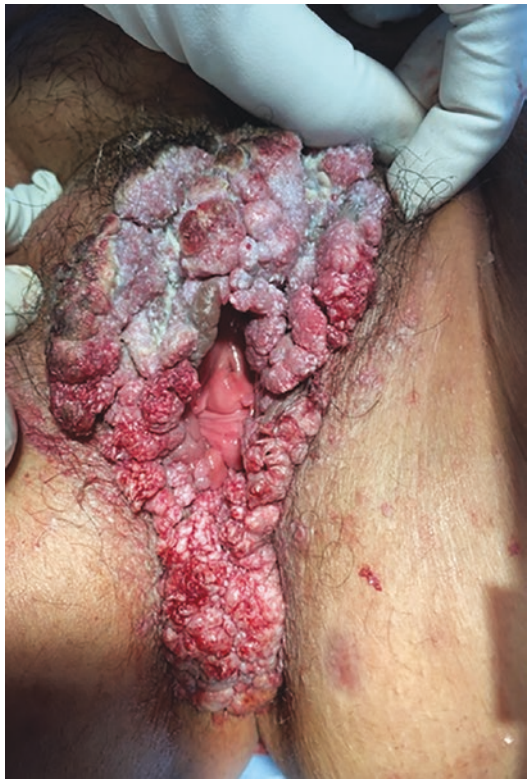


Fig. 25.1 12 cm exophytic fungating tumour over the left labia, right labia and perianal region. The mass did not infiltrate into the urethra, vagina, anal sphincters or rectum

However, most verrucous carcinomas are slow-growing, locally invasive tumours and the incidence of metastasis to the lymph nodes is low [2–5].

A high index of suspicion in women with a condyloma (genital wart) which fails to respond to usual treatment or which displays signs of ulceration is key for a prompt diagnosis [1].

Q: How Are Verrucous Carcinomas Managed?

The treatment paradigm for verrucous carcinomas involves an excision of the tumour with the aim of achieving clear microscopic margins. The resulting defect may be substantial depending on the size of the tumour and plastic flap reconstruction should be considered to cover the defect and restore the functional and cosmetic integrity.

Staging of the inguinofemoral lymph nodes is not warranted in most cases in view of the low risk of metastatic spread. However, verrucous carcinomas may co-exist with SCC in about 15% of cases and a sentinel lymph node biopsy or lymphadenectomy is indicated in addition to the excision of the tumour in these women [6].

Case 2: Bartholin Gland Tumours

Age, PS	36 years, P2 + 0, ECOG −1
Clinical presentation	Mass in perineal region associated with pain History of previous Bartholin's abscess Examination: 2 × 1.5 cm hard, non-mobile tender nodule on the right labia majora over the site of the Bartholin's gland. The lesion did not appear to invade into the anal sphincters or rectum. No clinical signs of inguinal lymphadenopathy
Co morbidities	Nil
MRI	Contrast-enhancing lesion which was highly suspicious for a Bartholin gland tumour
Surgery	Excision of the lesion, followed by bilateral inguinal lymphadenectomy
Histology	Squamous cell cancer Bartholin gland, margins free of tumor, no LVSI, lymph nodes negative

Q: What Are the Signs and Symptoms Associated with a Bartholin Carcinoma?

Cancer of the Bartholin's gland is extremely rare and accounts for less than 5% of all vulvar carcinomas. The age of onset is around 50 years and most cases usually affect postmenopausal women [7]. The histopathology of a Bartholin gland carcinoma is depends on the structure it arises from that is squamous or papillary (from the duct) or adenocarcinomas (from the gland) [8]. In half of cases, the tumours are squamous cell carcinomas [8].

Although a vulval mass is the most common presenting complaint, the diagnosis is often ambiguous not only because of the non-specific clinical manifestations namely symptoms such as dyspareunia, pain, itch or bleeding but also because the nodule is often erroneously presumed to represent a Bartholin's cyst or abscess. This may contribute to a delay in the diagnosis as these women will often undergo marsupialisation or simple excision of the Bartholin's gland in the first instance. Clinicians should therefore consider the probable diagnosis of an underlying malignancy in any postmenopausal woman with a Bartholin's gland swelling [9].

Q: What Is the Prognosis?

These cancers are usually diagnosed at advanced stages (III and IV) and are commonly associated with metastatic disease [10]. As for most vulval cancers, the presence of lymph node involvement is the most significant prognosticator [8]. Other predictors of oncological outcomes include tumour size and location.

Q: What Investigations are Usually Requested Preoperatively?

An MRI scan is particularly useful to determine the extent of local invasion into surrounding structures and to assess for any radiological evidence of lymphadenopathy. It is also useful in differentiating Bartholin gland carcinomas from cysts or abscesses [11].

A staging CT scan may be helpful to assess for disseminated disease when contemplating curative surgery in women with palpable inguinal lymph nodes.

Q: How Are Malignant Tumours of the Bartholin Gland Managed?

The mainstay of treatment for Bartholin's carcinoma involves surgical excision of the lesion. A re-excision should be considered if the margins are involved. In view of its position deep in the labia majora, extensive dissection into the ischiorectal fossa to attain clear margins may sometimes be necessary. If this poses a risk to the integrity of the anal sphincter or rectum, neoadjuvant chemoradiotherapy should be considered in the first instance [9]. Ipsilateral or bilateral lymphadenectomy is recommended for lateral or central tumours respectively. There is a lack of evidence regarding the role of inguinal sentinel lymph node biopsies (SLNB) and these are not validated in Bartholin's carcinomas [9].

Women may require radiotherapy to the vulva and inguinal lymph nodes postoperatively. These reduce the incidence of local recurrence from 27% to 7% [9].

Case 2: She did not receive any adjuvant treatment and remained under surveillance.

Case 3: Vulval Melanomas

Age, PS	72 years, P1 + 0, ECOG −1
Clinical presentation	Complaints of swelling and itch over the vulva. Examination reveals a 3x2cm pigmented lesion over the right labia majora. No palpable inguinal nodes. A systematic examination does not reveal any other lesions over the rest of the body
Co morbidities	Hypertension
Biopsy	Nodular melanoma, Clark's level IV
PET CT, MRI brain	No evidence of distant metastasis/ extravulval disease
Surgery	Excision of the lesion and an ipsilateral groin SLNB.
Histology	Nodular melanoma, margins are clear and the lymph node is negative for metastasis. Stage 1B

Q: How Do Women with Vulval Melanoma Usually Present?

Vulval melanomas (VM) are rare and account for 0.5% of all female genital cancers. It is the second

most common type of vulval cancer after VSCC and represents up to 10% of all vulval cancers. The median age of diagnosis is 67 years but VM may also occur in younger women [12]. Primary lesions are highly variable in appearance and may present as nodules with altered pigmentation and irregular borders, with or without ulceration. The most common symptoms include a vulval mass, pain, bleeding, itch or irritation. Some women may also be asymptomatic. The pathogenesis of VM is poorly understood and the role of chronic inflammatory conditions such as lichen sclerosis or infections with HPV remains unclear [12].

Q: What Is the Prognosis for VM?

Cancer cells may spread locally, via the lymphatics but also via the haematogenous route to other organs such as the lung, liver, bones and brain. The incidence of regional lymph nodes involvement ranges from 9% to 23% [13].

Compared to cutaneous melanomas, VM has a poor prognosis with a 5-year survival rate of 58% [9]. Different recognised histotypes include the superficial spreading melanomas (40–58%), mucosal lentiginous (27–57%), nodular (22–28%) and unclassified (12–16%). Nodular VM are the most aggressive and have a poorer prognosis [14].

Q: What Variables Are Associated with Oncological Outcomes?

Tumour size was found to be the only significant predictor for local VM recurrence [9].

Multiple staging systems have been proposed to prognosticate the risk of distant recurrence for VM. These include Breslow's thickness (Table 25.1), Clark level of melanoma invasion and Chung's modified classification (Table 25.2). To date, the American Joint Committee on Cancer (AJCC) staging system (Table 25.3) appears to be the most useful predictor of recurrence free survival for VM [15]. It includes prognostic factors namely tumour thickness, ulceration, regional lymph node status, site of distant disease spread and serum lactate dehydrogenase levels. Overall, advanced stage of disease, Breslow thickness >1 mm, ulceration, and mitotic index >1/mm^2 constitute poor predictors of survival while younger age may have a protective role.

The FIGO staging is not helpful in decision-making in women with VM.

Table 25.1 Breslow Staging for Vulval melanoma

Stage	Depth of Epidermal infiltration/mm
I	≤ 0.75
II	0.76–1.5
III	1.51–2.25
IV	2.26–3.0
V	>3

Table 25.2 Clark and Chung modified classification of Vulval melanoma

Level	Clark	Chung
I	In situ melanoma: All tumor is above the epidermal basement membrane	In situ melanoma: all tumor is above the epidermal basement membrane
II	Tumor extends through BM into PD	Tumor invasion = 1 mm
III	Tumor fills PD and extends to RD but does not invade it	Tumor invasion = 1-2 mm
IV	Tumor extends into the RD	Tumor invasion>2 mm
V	Tumor extends into subcutaneous fat	Tumor extends into subcutaneous fat

Abbreviations: BM-basement membrane, PD- papillary dermis, RD- reticular dermis

Table 25.3 AJCC staging for Vulval melanoma

Stage	T	N	M
0	In situ	0	0
IA	<1 mm, no ulceration/Clark's II and III	0	0
IB	<1 mm, ulceration/Clark's IV and V 1.01–2 mm, no ulceration	0	0
IIA	1.01–2 mm, ulceration 2.01–4 mm, no ulceration	0	0
IIB	2.01–4 mm, ulceration >4 mm, no ulceration	0	0
IIC	>4 mm, ulceration	0	0
IIIA	Any thickness, no ulceration	1 node micrometastases	0
IIIB	Any thickness, ulceration Any thickness, no ulceration Any thickness +/− ulceration	1 node micrometastases Up to 3 node micrometastases In transit met/satellites+ nodes	0
IIIC	Any thickness, ulceration Any thickness +/− ulceration	Up to 3 nodes macrometastases >metastatic nodes/matted nodes/in transit nodes	0
IV	Any thickness	Any nodes	+

Q: What Molecular Mutations Are Prevalent in Vulvovaginal Melanomas?

The most common mutation in VM arises in the cKIT gene and these are present in up to 35% of cases [13]. KIT is a receptor tyrosine kinase that promotes cell growth and proliferation. BRAF and NRSA mutations can also occur more rarely [16]. BRAF V 600 (BRAF mutation at 600th codon) mutations are associated with sensitivity to BRAF and MEK inhibitors. Mutational analysis is thus recommended in view of the emerging role of immunotherapy agents in cancer treatment (see below).

Q: What Investigations Should Be Requested?

A total body examination is necessary to exclude other primary sites of cancer. VM are often diagnosed in advanced stages and a staging CT scan, including a head CT scan are required given the high risk of lymphatic and haematogenous spread [9].

Q: How Are Women with VM Managed?

All women newly diagnosed with VM should be discussed at both the gynaeoncology MDT and the melanoma MDT meetings.

Surgical Excision

Wide local excision with negative free margins remains the mainstay of treatment. There is no evidence that radical surgery confers any survival benefit and conservative surgical excision to achieve microscopically free margins appears to be adequate and safe in reducing the risk of locoregional recurrence in VM [13, 17]. If the margins are involved, a re-excision is normally recommended.

Staging Inguinofemoral SLNB is now considered the gold standard in women with VM and may guide further therapies [18]. The therapeutic benefit of completion lymphadenectomy in cases of positive SLN remains unclear however may offer better disease control if residual tumour is completely resected.

Radiotherapy

Cutanous melanomas tend to be relatively radioresistant and radiotherapy thus has a limited role in the treatment of VM. It is often used as an adjunct in cases where surgical margins are involved or when the lesion is deemed to be unresectable. Radiotherapy may potentially have a role in locoregional symptom control, particularly for palliation, but it does not appear to confer any survival benefit in cases of distant recurrence.

Immunotherapy [19]

It has a role in metastatic or recurrent or unresectable disease. Combination check point blockade with Anti PD1 and monoclonal antibodies (Nivolumab/ipilimumab) or Anti PD-1 monotherapy is the first line therapy to be considered. Other recommended category 1 regimens in BRAF mutated tumours are, BRAF/MEK inhibitor combination therapy i.e. Dabrafenib/ trametinib, Vemurafenib/ cobimetinib and Encorafenib/ binimetinib. For activating mutations of KIT – KIT inhibitor therapy (e.g., imatinib, dasatinib, nilotinib, ripretinib) may be used as second line systemic therapy.

Case 3: Case is discussed at the melanoma MDT and she remains under close surveillance.

Case 4: Basal Cell Carcinoma

Age, PS	51 years, P1 + 0, ECOG −1
Clinical presentation	Complaints itching and irritation over the vulva × 12 months Examination: 1.5 cm firm vulvar lesion with shallow red ulcerations over left labia majora. No palpable inguinal nodes
Co morbidities	Nil
Biopsy	Basal cell carcinoma (BCC)
PET CT, MRI brain	No evidence of distant metastasis/ extravulval disease
Surgery	Wide local excision
Histology	Basal cell carcinoma, clear margins

Q: What Are the Common Signs and Symptoms Associated with BCCs?

BCC of the vulval often occur over the labia majora and affects women between 40 to 90 years old (mean age 80) [20]. Most women will present with pruritus or a new lump. BCC are rare (~5% of all vulval cancers) and behave in a locally invasive fashion. They only tend to spread to the regional lymph nodes in cases of large and invasive tumours [21].

Q: How Are Women with BCCs Managed?

BCC have an excellent prognosis and very rarely metastasise to distant sites [21]. Imaging is not required pre-operatively unless there is evidence of lymphadenopathy [9]. Wide local excision with microscopically free margins is usually curative and lymph node staging is not mandated, except in cases of clinically enlarged groin lymph nodes. There is no benefit of adjuvant radiotherapy on recurrence rate or overall survival.

Case 4: She did not require any further treatment and remains under 6-monthly surveillance.

Case 5: Vulval Paget's Disease

Age, PS	84 years, P1 + 0, ECOG −2
Clinical presentation	Complaints of persistent itch over the pubic area, refractory to topical steroids × 18 months Examination: A white plaque with hyperkeratosis extending across both labia bilaterally is noted
Co morbidities	Ischaemic heart disease, hypertension, chronic kidney disease
Biopsy	Invasive vulval Paget's disease
Treatment	In view of her age and co-morbidities, she declined any surgical treatment. She was therefore treated with a course of imiquimod 5% and had a good response to it. She remains under surveillance

Q: What Are the Clinical Features of Vulval Paget's Disease?

Extramammary Paget's disease (EMPD) is a rare condition and accounts for 1–2% of anogenital cancers [13]. It usually affects postmenopausal women [22]. An associated occult malignancy may be present in 12–33% of cases [23]. Invasive vulval Paget's disease (VPD) can be primary (75–95%) or secondary (25%).

In invasive primary VPD, the cancer is believed to arise from the apocrine glands or keratinocytes of the epidermis itself while in secondary VPD, invasion of the overlying skin originates from an adenocarcinoma of the Bartholin's gland or more rarely, vaginal, colorectal, urothelial or cervical tumours [13, 24].

The primary lesion typically presents with an erythematous, eczematous, plaque with white scaling. Patients may be asymptomatic or present with an itch or irritation. The size of the lesion may vary from a few centimetres to an extensive lesion involving the entire perineum, perianal or pubic territories.

Q: What Is the Prognosis of Women with VPD?

The prognosis for superficial invasive primary Paget's disease i.e., cases which do not invade beyond the epidermis are excellent. The width and depth of invasion have a negative correlation with survival. Other possible prognosticators include clitoral involvement, raised serum CEA levels and lymph node metastases [25].

Q: How Are Women with VPD Managed?

A biopsy should be pursued to confirm a diagnosis of VPD in women with the above symptoms.

Surgical Excision

Surgery constitutes the mainstay of treatment. Unfortunately, VPD is often multifocal and a large proportion of women will require multiple resections which may result in cosmetic and functional alterations [13]. Regional lymph node staging is recommended in cases of invasive VPD where the depth of invasion is over 1 mm deep or when there are clinically enlarged lymph nodes. Sentinel lymph node biopsies have not been validated for women with VPD.

Radiotherapy

Radiotherapy is an acceptable treatment alternative for patients who are unfit to undergo surgical resection. Adjuvant radiotherapy has also been associated with a lower rate of locoregional recurrence [13].

Imiquimod 5%

Imiquimod is a topical immunomodulatory and its use has been reported to induce resolution of superficially invasive VPD [26]. Imiquimod therefore represents an acceptable non-surgical option for women who would otherwise necessitate demolitive surgery.

Topical Chemotherapeutic Agents

5-fluorouracil, bleomycin and trastuzumab in combination with paclitaxel have previously been tested with varying efficacy. Their safety and efficacy should be explored in randomised controlled trials [13].

Key Points

1. Surgery is the mainstay of treatment in rare vulval histologies. Radiotherapy may be used as adjunctive treatment in some cases
2. Sentinel lymph node biopsy has not been validated in bartholin gland carcinoma and paget's disease. Verrucous carcinoma and basal cell carcinoma have very low risk of metastatic lymph nodal spread.
3. The FIGO staging is not helpful in decision-making in women with VM. American Joint Committee on Cancer (AJCC) staging system (Table 25.3) appears to be the most useful predictor of recurrence free survival for VM

4. Immunotherapy has an important role in of vulval melanomas, hence molecular classification is recommended

References

1. Campaner A, Cardoso F, Fernandes G, Veasey J. Verrucous carcinoma of the vulva: diagnosis and treatment. An Bras Dermatol. 2017;92(2):243–5.
2. Nascimento A, Granter S, Cviko A, Yuan L, Hecht J, Crum C. Vulvar acanthosis with altered differentiation: a precursor to verrucous carcinoma? Am J Surg Pathol. 2004;28(5):638–43.
3. Yorganci A, Serinsoz E, Ensari A, Sertcelik A, Ortac F. A case report of multicentric verrucous carcinoma of the female genital tract. Gynecol Oncol. 2003;90:478–81.
4. Spiro RH. Verrucous carcinoma, then and now. Am J Surg. 1998;176:393–7.
5. Hoang L, Park K, Soslow R, Murali R. Squamous precursor lesions of the vulva: current classification and diagnostic challenges. Pathology. 2016;48:291–302.
6. Liu G, Li Q, Shang X, et al. Verrucous carcinoma of the vulva: a 20 year retrospective study and literature review. J Low Genit Tract Dis. 2016;20:114–8.
7. Leuchter R, Hacker N, Voet R, Berek J, Townsend D, Lagasse L. Primary carcinoma of the Bartholin gland: a report of 14 cases and review of the literature. Obstet Gynecol. 1982;60:361–8.
8. Hill D, Butterfield A. Bartholin's gland squamous cell carcinoma, a rare vulvar neoplasm. J Diagn Med Sonogr. 2010;26(6):296–8.
9. Morrison J, Buckley L, Baldwin P, Cogswell L, Edey K, Faruqi A, et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2020;252:502–25. https://www.bgcs.org.uk/wp-content/uploads/2021/07/BGCS-vulval-guidelines-v22.pdf
10. Bhalwal A, Nick A, Dos Reis R, et al. Carcinoma of the Bartholin gland: a review of 33 cases. Int J Gynecol Cancer. 2016;26(4):785–9.
11. Hosseinzadeh K, Heller M, Houshmand G. Imaging of the female perineum in adults. Radiographics. 2012;32(4):E129–68.
12. Moxley K, Fader A, Rose P, et al. Malignant melanoma of the vulva: an extension of cutaneous melanoma? Gynecol Oncol. 2011;122:612–7.
13. Di Donata V, Donfrancesco C, Casorelli A, Benedetti PP. Other diseases of vulva (Paget's, melanoma and sarcoma). In: Ayhan A, Reed N, Gultekin M, Dursun P, editors. Textbook of gynaecological oncology. 3rd ed. ESGO; 2016. p. 931–9.
14. Campaner A, Fernandes G, Cardoso F, Veasey J. Vulvar melanoma: relevant aspects in therapeutic management. An Bras Dermatol. 2017;92(3):398–400.
15. Balch C, Buzaid A, Soong S, et al. Final version of the American joint committee on cancer staging system for cutaneous melanoma. J Clin Oncol. 2001;19:3635–48.
16. Aulmann S, Sinn H, Penzel R, et al. Comparison of molecular abnormalities in vulvar and vaginal melanomas. Mod Pathol. 2014;27(10):1386–93.
17. Iacoponi S, Rubio P, Garcia E, et al. Prognostic factors of recurrence and survival in vulvar melanoma: subgroup analysis of the VULvar CANcer study. Int J Gynecol Cancer. 2016;26(7):1307–12.
18. Trifiro G, Travaini L, Sanvito F, et al. Sentinel node detection by lymphoscintigraphy and sentinel lymph node biopsy in vulvar melanoma. Eur J Nucl Med Mol Imaging. 2010;37:736–41.
19. NCCN clinical practice guidelines in oncology. Vulvar cancer. Version 1.2023-Dec 22, 2022. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf.
20. de Giorgi V, Salvini C, Massi D, Raspollini M, Carli P. Vulvar basal cell carcinoma: retrospective study and review of literature. Gynecol Oncol. 2005;97(1):192–4.
21. Feakins R, Lowe D. Basal cell carcinoma of the vulva: a clinicopathologic study of 45 cases. Int J Gynecol Pathol. 1997;16(4):319–24.
22. Delport E. Extramammary Paget's disease of the vulva: an annotated review of the current literature. Australas J Dermatol. 2013;54:9–21.
23. Gavriilidis P, Chrysanthopoulos K, Gerasimidou D. Extramammary Paget's disease of the vulva. Case Reports. 2013;2013:bcr2013200623.
24. Stroup A, Harlan L, Trimble E. Demographic, clinical, and treatment trends among women diagnosed with vulvar cancer in the United States. Gynecol Oncol. 2008;108(3):577–83.
25. Terlou A, Blok L, Helmerhorst T, et al. Premalignant epithelial disorders of the vulva: squamous vulvar intraepithelial neoplasia, vulvar Paget's disease and melanoma in situ. Acta Obstet Gynecol Scand. 2010;89:741–8.
26. van der Linden M, Meeuwis KA, Bulten J, Bosse T, van Poelgeest M, de Hullu J. Paget disease of the vulva. Crit Rev Oncol Hematol. 2016;101:60–74.

Part VI

Case Based Studies: Cancer in Pregnancy

26

Management of Gynaecological Malignancies in Pregnancy: Borderline Ovarian Tumor, Ovarian Cancer

Dawn Parris, Nadiah Arrifin, and Ashwini Bilagi

Introduction

Although a diagnosis of cancer is uncommon in pregnancy, the incidence is increasing and across all malignancies, there is an incidence of 1 in 1000 pregnancies which includes breast, bowel, melanoma as well as gynaecological cancers [1]. However, the true incidence remains difficult to estimate as obstetric and oncological databases are not streamlined and do not communicate with each other. This means that the diagnosis of cancer during pregnancy, or particularly postnatally, could be missed from obstetric databases. This has led to the creation of the International Network on Cancer, Infertility and Pregnancy. This network aims to lead to advances in the management of women with cancer in pregnancy along with facilitating large-scale studies. Currently, it comprises of 62 centres from 25 countries with over 2000 patients with a cancer diagnosis during pregnancy [2].

Ovarian tumours are detected in 0.2–8.8% of all pregnant women; majority being benign namely dermoid cysts, cystadenomas, corpus luteum etc. Ovarian cancers are seen in 6–10% cases of all persistent ovarian tumours out of which germ cell and borderline cancers are more common [3].

Treatment of women with cancer in pregnancy can be challenging and care is often individualised with a multi-disciplinary team approach, considering the primary origin, stage and grade of the cancer as well as a woman's gestation and her background medical conditions. In this chapter we shall discuss the cases pertaining to ovarian malignancy in pregnancy.

Case 1: Borderline Ovarian Tumour

Age, PS, BMI	25 years, G2P1 previous one cesarean, ECOG −1, BMI = 32
Presenting complaints	Presented at 18/40 period of gestation with ultrasound diagnosis of solid cystic 10 cm mass in the right ovary Past history of ovarian cystectomy for a serous borderline ovarian tumour 2 years back
Co morbidities	Chronic hypertension
Ultrasound abdomen and pelvis	Single live fetus 17+ 6 weeks multi-loculated right ovarian mass, septal thickness 2-5 mm, moderately increased vascularity
Tumor markers	CA125: 125 U/ml

D. Parris (✉) · N. Arrifin · A. Bilagi
Obstetrics and Fetal Medicine Department, Birmingham City Hospital, Sandwell and West Birmingham Hospitals, Birmingham, UK
e-mail: Dawn.parris1@nhs.net; a.bilagi@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_26

Q: What Investigations Are Required To Aid Management?

Transvaginal ultrasound has been widely considered as the gold standard imaging method to investigate adnexal masses in early pregnancy including borderline ovarian masses [4, 5]. Unilocular solid projections with irregular and vascularised papillary projections are suggestive of borderline ovarian tumour (Fig. 26.1). Ultrasound assessment of the adnexae is routine in pregnancy. However, the gravid uterus, particularly after 20 weeks' gestation, can lead to limitations in the evaluation of the adnexae [4]. MRI can be used from 12 weeks' gestation in cases of indeterminate adnexal mass [5]. Computed tomography and PET CT scan are not recommended as they expose the fetus to high dose of radiation.

CA125 does not have much role as levels are elevated during pregnancy, however very high levels may indicate malignancy or widespread disease.

Q: What Is the Plan of Management?

Multi-disciplinary team involvement is absolutely vital in pregnant women with suspected borderline ovarian tumours. Close liaison is quintessential between gynaecologists, gynaecology oncological surgeons, obstetricians with an interest in maternal medicine, radiologist, histopathologist and, depending on the gestation, liaisonwith neonatologist. Fertility preserving surgery is usually advised for BOT in premenopausal women as majority are diagnosed in young women [5].

Management in pregnancy should be individualised with factors to consider including gestation, size and stage of the tumour and desire for future fertility.

The timing and approach of surgical management – whether to be performed in pregnancy or to be delayed until caesarean section or postnatally, and laparoscopy or laparotomy – will depend on many factors including gestation and stage. Second trimester of pregnancy is a safe time to perform surgery as the risk of miscarriage is minimized. Laparoscopy is safe to perform and has similar complication rate as laparotomy, however much depends on the surgical expertise. Endobag retrieval is mandatory during laparoscopy as in non-pregnant cases. Staging laparotomy with peritoneal cytology, unilateral salpingo-oophorectomy and peritoneal biopsies from suspicious areas is the preferred option. Ovarian cystectomy during pregnancy is difficult to perform because of pregnancy related hypervascularity and risk of bleeding and hematoma formation; but can be done if tumours are bilateral. Care should be taken to minimize uterine handling, ensure adequate hemostasis and careful use of cautery.

Q: What Is the Prognosis?

Pregnancy is not thought to worsen the prognosis of borderline ovarian tumours, even in cases of recurrence [4]. Borderline ovarian tumours (BOT) can recur 10 years after previous surgery for BOT, and may later develop into low grade serous tumours or ovarian mucinous adenocarcinomas, hence a close follow up is recommended.

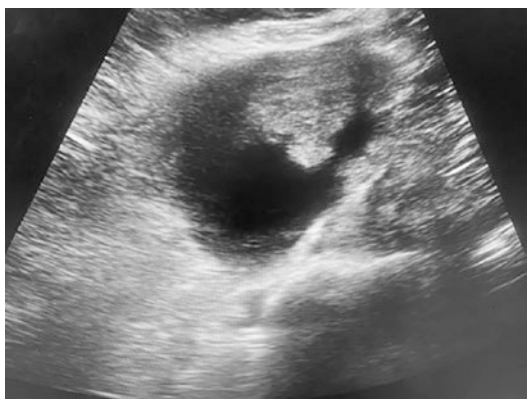


Fig. 26.1 Serous borderline ovarian tumorwith solid area and papillary projection

The patient underwent staging laparotomy-right salpingo oophorectomy at 20 weeks' gestation. The final histopathology was serous borderline ovarian tumour with microinvasion. The plan is to keep the patient on close follow up.

Case 2: High Grade Serous Ovarian Cancer

Age, PS, BMI	28 years, primigravida, ECOG −1, BMI = 32
Presenting complaints	Presented at 24/40 period of gestation abdominal distension, a five-day history of abdominal pain and breathlessness. Past history of ovulation induction
Co morbidities	Gestational diabetes on insulin
Ultrasound abdomen and pelvis	Single live fetus 22+ 6 weeks,Right ovarian mass measuring about 8 cm with solid and cystic components with marked vascularity and ascites
MRI abdomen + pelvis	8 cm ovarian mass with peritoneal nodularity with 1–2 cm diameter sub diaphragmatic tissues deposits along with omental cake
Image-guided biopsy:	High grade serous ovarian carcinoma

Q: What Should Be the Further Management of Ovarian Malignancy?

Surgery and chemotherapy remain the mainstay of management of a high-grade epithelial ovarian cancer. It is an extremely difficult clinical situation in a primiparous with a possible viable fetus and an advanced stage ovarian cancer. A careful multidisciplinary approach involving gynaecological oncologists, medical oncologists, specialist nurses, obstetricians and anaesthetists and neonatologists should be considered. Careful patient counselling regarding the ovarian cancer, its stage, its prognosis and impact of treatment on pregnancy is crucial. Discussion should be done with medical oncologist regarding choice of chemotherapy during pregnancy and its impact on pregnancy and the fetus. Timing for surgery is also tailored around fetal viability and response to chemotherapy.

In the first trimester, following appropriate counselling; women may choose to elect for termination of pregnancy prior to standard surgical and chemotherapeutic management. In the second and third trimesters, pregnancy-preserving strategies may be warranted. Chemotherapy can be delayed till this gestation to minimise the teratogenic effects. The safest window for surgery is usually regarded as second trimester but is only for early stage where a conservative surgery with adnexectomy is regarded as safe as placenta takes over all the hormonal support for pregnancy from 14 weeks gestation and removal of adnexae does not adversely impact continuation of pregnancy. Restaging and completion surgery after delivery may be considered in early stage ovarian cancer.

However, trauma of a surgical intervention during any gestation can instigate preterm labour and therefore care and precautions like rest, tocolytics and steroids maybe considered. The administration of intramuscular corticosteroids for fetal lung maturation should be considered 48 h preoperative if surgery is planned between 24 and 34 weeks of gestation. Although the use of prophylactic tocolytics remains controversial the literature suggests some benefit of these in reducing preterm labour [6].

Advanced cases of EOC as in this patient are rare and pose a bigger dilemma. The preferred strategy is diagnostic laparoscopy or image guided biopsy followed by neoadjuvant chemotherapy and radical debulking surgery after delivery. Extensive cytoreductive surgery for advanced stage ovarian cancer is preferably performed as closer to third trimesteras possible or preferably postnatally and is likely to require pelvicclearance(hysterectomy+bilateralsalpingo-oopherectomy+omentectomy+removal of any other visible site of disease.

Intraoperatively, additional anaesthetic and surgical considerations should be taken to minimise risk and harm to the mother and the foetus. At induction of anaesthesia, the patient should be placed in the left lateral position to reduce aortocaval compression. Careful attention should be paid to optimising maternal respiratory and cardiovascular parameters to minimise the risk of intrauterine hypoxia, which may have potentially serious consequences to the fetus.

Postoperatively, a Kleihauer test should be performed if the maternal rhesus status is negative and appropriate anti-D prophylaxis administered. Patients should be assessed for appropriate thromboprophylaxis with grade II compression

stockings and the use of subcutaneous low molecular-weight heparin.

What Should Be the Further Management of the Pregnancy?

The pregnancy should be followed up regularly in the antenatal clinic and serial growth scans may be indicated to monitor fetal growth and well-being, especially if chemotherapeutics are being used. Doppler studies of the fetal cerebral artery peak systolic velocity can be useful in monitoring for fetal anaemia. Timing and mode of delivery should be planned around surgical and chemotherapeutic modalities of treatment used in each individual case. Good nutrition and psychological support are important throughout pregnancy.

What Is the Effect of Chemotherapy on Fetal Outcome?

The physiological changes in the renal and cardiovascular systems during pregnancy can alter the pharmacodynamics of chemotherapeutic drugs and thus altered absorption, distribution and clearance of these drugs should be accounted for in dosing.

Chemotherapy is associated with a higher rate of pregnancy loss and teratogenesis thus should be avoided in the first trimester. Taxane and platinum-based therapies are the mainstay of chemotherapy for ovarian cancer and have been shown to be linked to up to 25% rate of teratogenesis in the first trimester, compared to 1.3% risk when used in the later two trimesters of pregnancy [7]. Platinum exposure in pregnancy nonetheless still carries the risk of featl growth restriction, preterm birth, neonatal ARDS, neonatal anaemia and pancytopenia; whilst taxane exposure has been linked theoretically to toxicity of the nervous, digestive and respiratory systems although there is evidence of only minimal transplacental transfer to the fetus. These risks should be relayed to mother in the process of shared decision-making about treatment and should be borne in mind when timing the treatment – the literature suggests a 3 week interval between last chemotherapy and delivery as a safe window to minimise the risk of myelosuppression in the mother and the neonate.

There remains little experience in the use of newer targeted agents like immunotherapeutic and anti-angiogenic factors in pregnancy, and more research is required to establish their safety and efficacy. Intraperitoneal chemotherapy is contraindicated in pregnancy.

Q: What Is the Likely Prognosis and Outcome?

Most common adverse events reported with ovarian cancer in pregnancy are prematurity, miscarriage and fetal growth restriction (FGR). Advanced stage, undifferentiated histology are the adverse prognostic factors. The literature suggests that ovarian cancer is diagnosed and thus treated at an earlier stage (Stage I: 63%) in pregnancy, accounting for better survival. In a systematic review of 105 pregnancies with EOC, live birth rate was 81.3%, more than half delivered at term out of which 71% were by caesarean section [8]. There was no significant difference in FGR rates in patient with or without chemotherapy [8].

Case 3: Germ Cell Tumour

Age, PS, BMI	28 years, G3P2 previous two cesarean, ECOG −1, BMI = 32
Presenting complaints	Presented at 20/40 weeks' gestation history of abdominal pain for 5 days
Co morbidities	Nil
Ultrasound abdomen and pelvis	Single live fetus 19+ 5 weeks 14 cm; left ovarian heterogeneous mass with solid cystic areas
MRI abdomen + pelvis	14 cm ovarian mass – solid with haemorrhage inside the mass. No pelvic lymphadenopathy
Tumor markers	CA-125:189 U/ml, LDH: 500 U/L, AFP: 5 ng/ml, bHCG: 2 mIU/ml

Q: What Is the Reliability of Tumour Markers in Pregnancy?

The role of tumour markers is limited in women diagnosed with cancer during pregnancy due to their low specificity. They will often be found to be elevated however this is commonly a result of the physiological changes of pregnancy. BhCG is produced by the trophoblast while AFP is produced by the liver of a developing fetus which passes into the maternal circulation. Both BhCG and AFP can be raised in germ cell tumours outside pregnancy however, as demonstrated; the levels in pregnancy will be raised physiologically meaning that they should be interpreted with caution. Similarly, CA-125 is present in relatively high concentrations in amnion and decidual cells, and amniotic fluid, thus explaining the often high readings encountered in normal pregnancy [9]. It is produced by the decidual and granulosa cells especially in first and last trimester of pregnancy.

Tumour markers can also be raised due to obstetric complications such as high LDH levels arising from pre-eclampsia or HELLP. However, the reference ranges of some tumour markers will remain the same in pregnancy including LDH. Therefore, treatment should not be based solely on tumour marker levels in pregnancy [10].

Q: What Is the Further Management?

The management of ovarian masses in pregnancy is similar to that outside pregnancy however accounting for maternal and fetal considerations such as gestation. Fertility sparing surgery is appropriate in these women if diagnosed at an early stage and with low grade disease. Surgical management should ideally be performed in the second trimester in order to decrease the risks of ovarian torsion, rupture, pregnancy loss or delay the diagnosis of malignancy.

Indications of adjuvant chemotherapy in germ cell tumours are similar to non-pregnant patients. This includes dysgerminoma stage II – IV, immature teratoma stage II – IV or stage I grade 2–3, embryonal or endodermal sinus tumour of any stage and recurrence following any previously treated early stage germ cell tumour like stage IA dysgerminoma or stage IA grade 1 immature teratoma.

The standard regime for adjuvant chemotherapy is BEP (bleomycin, cisplatin and etoposide) for 3–4 cycles. Chemotherapy should be avoided in the first trimester due to the high teratogenic risk – 25% with combination chemotherapy and 10% with single agent.

Q: What Are the Fetal and Maternal Outcomes in Germ Cell Tumours Complicating Pregnancy?

Many women diagnosed with ovarian tumours in pregnancy have good outcomes as the diagnosis is often made at an early stage and with low grade disease. There are reports of rapid growth and recurrence of germ cell tumours however. Women should therefore undergo comprehensive surgical staging at the time of diagnosis. Overall, the prognosis is good even with malignant ovarian germ cell tumours provided that the woman receives treatment without delay with combination chemotherapy [9]. The relapse rate after fertility sparing surgery (unilateral salpingo-oophorectomy) in stage IA dysgerminoma is between 10–20%. The overall survival rate is 90–100% [9, 11].

Fetal outcomes are generally good. The preterm delivery rate in malignant ovarian germ cell tumours is 43%. Fetuses are at risk of intrauterine growth restriction (22.8%). Exposure to chemotherapy (after the first trimester) does not appear to increase the chances of FGR significantly. The theorised mechanism for the increased risk of FGR without chemotherapy is due to rapid tumour growth and large tumour size (17.9 cm mean size), a reduction in placental perfusion may account for this association [12].

Patient underwent staging laparotomy + Left salpingo-oophorectomy at 22 weeks gestation. The final histopathology was Dysgerminoma confined to the ovary, capsule intact. The patient is on close follow up.

Keypoints

- Cancer in pregnancy is a complex clinical situation needing careful evaluation and indivualised planning of care by a multidisciplinary team consisting of gynaecological oncologist, medical oncologist, radiologist, histopathologist, obstetrician and neonatologist and clinical nurse specialist
- Management of cancer should be postponed to beyond period of fetal viability(>24 weeks gestation) only if it is unlikely to impact prognosis of cancer.
- Ovarian masses are advised to be removed after 14 weeks gestation once placental functions are established.
- Neoadjuvant chemotherapy can be administered during pregnancy for advanced stage epithelial ovarian cancer. Cytoreductive surgery can be performed with caesarean section after fetal viability is reached to allow safe survival of the baby

References

1. China S, Sinha Y, Sinha D, Hillaby K. Management of gynaecological cancer in pregnancy. Obstet Gynaecol. 2017;19:139–46.
2. Amant F, Bervellier P, Boere IA, Cardonick E, Fruscio R, Fumagalli M, et al. Gynaecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019;30:1601–12.
3. Giuntoli RL, Vang RS, Bristow RE. Evaluation and management of adnexal masses during pregnancy. 2011; 26(12): 3456-65. Clin Obstet Gynecol. 2006;49(3):492–505.
4. Vidal Urbinati AM, Iacobone AD, Di Pace RC, Pino I, Pittelli MR, Guerreri ME, et al. Borderline ovarian tumour in pregnancy: can surgery wait? A case series. Arch Gynaecol Obstet. 2021;304:1561–8.
5. Zilliox M, Lecointre L, Azais H, Ballester M, Bendifallah S, Bolza PA, et al. Management of borderline ovarian tumours in pregnancy: result of French multi-centre study. Eur J Obstet Gynecol Reprod Biol. 2021;256:412–8.
6. Bueno Moral AI, Vilches Jiménez JC, Serrano Olave A, Espejo Reina MP, Valdivia de Dios ME, Jiménez López JS. Advanced ovarian cancer during pregnancy. Tumour evolution analysis and treatment approach. Medicina (Kaunas). 2021;57(5):426.
7. Grimm D, Woelber L, Trillsch F, Keller-v.Amsberg G, Mahner S. Clinical management of epithelial ovarian cancer during pregnancy. Eur J Cancer. 2014;50(5):963–71.
8. Blake EA, et al. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2015;186:97–105.
9. De Haan J, Verheecke M, Amant F. Management of ovarian cysts and cancer in pregnancy. Facts Views Vis Obgyn. 2015;7(1):25–31.
10. Nan SH, Lotgerink A, MhallemGziri M, Van Calsteren K, Hanssens M, Amant F. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systemic review. BMC Med. 2012;10:86.
11. Wang L, Huang S, Sheng X, Ren C, Wang Q, Yang L, et al. Malignant ovarian tumours during pregnancy: a multicenter retrospective analysis. Cancer Manag Res. 2020;12:10841–8.
12. Kodama M, Grubbs BH, Blake EA, Cahoon SS, Murakami R, Kimura T, et al. Feto-maternal outcomes of pregnancy complicated by ovarian malignant germ cell tumor: a systematic review of literature. Eur J Obstet Gynaecol Reprod Biol. 2014;181:145–56.

Gestational Trophoblastic Disease

27

Amita Suneja and Rashmi Malik

Introduction

Gestational Trophoblastic Disease (GTD) is a group of disorders arising from trophoblastic tissue exhibiting benign, locally invasive or malignant lesions. Benign lesions include partial or complete mole having a malignant potential. The term Gestational Trophoblastic Neoplasia (GTN) is coined to malignant lesions like Invasive Mole, Choriocarcinoma and Intermediate Trophoblastic Tumors including Placental Site Trophoblastic Tumors/Epitheloid Trophoblastic Tumors (PSTT/ETT). Latest classification includes Atypical placental site nodule (APSN) as 15–20% may coexist with or develop into PSTT/ETT [1]. GTN has unique features - it always follows pregnancy event, may it be molar pregnancy, abortion, ectopic or normal pregnancy, it has very sensitive biomarker beta hCG; is highly chemo sensitive and can be cured even in advanced stages. Many recent developments in molecular biology and effective therapies have improved the survivals making it curable in all cases if properly managed.

Case 1 Molar Pregnancy

Age, Parity, PS	25 years P1 + 0; ECOG = 1, BMI 28 kg/m^2
Presenting complaints	Irregular vaginal bleeding × 1 months preceded by 3 months amenorrhea
Examination	Uterus enlarged to 18 weeks, bilateral fornices were free
Co morbidities	Nil
Ultrasound	USG: Mutiple cystic areas in uterine cavity s/o snow storm appearance Bilateral ovaries normal
Beta HCG	B hCG: 96,000 U/ml
Investigations	Hb%: 13 g%, platelets N, LFT, KFT: Normal
Provisional diagnosis	Molar pregnancy

Q1: How Will You Manage this Case?

She is a case of complete hydatiform mole (CHM) of 18 weeks uterine size. Suction evacuation is the method of choice for evacuation of molar pregnancy irrespective of uterine size.

Pre-evacuation evaluation includes thorough clinical examination, biochemical tests and imaging as given below:

(a) Ultrasound pelvis
(b) Serum quantitative β-hCG

A. Suneja (✉) · R. Malik
Obstetrics and Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_27

(c) Complete blood count, clotting studies (PT and PTT), renal and liver functions, blood group and cross matching to arrange blood
(d) Chest X-ray
(e) Thyroid function tests if signs and symptoms of hyperthyroidism are present

Evacuation

The procedure is usually performed under general or regional anaesthesia, however paracervical block may be used in patients with a small uterus. It should be done under ultrasound guidance and includes following steps:

(a) Serial dilation of cervix without sounding the uterus. The precaution is taken to introduce the dilator just beyond the internal os.
(b) Karman's cannula (12–14 mm) is introduced till beyond the internal os, suction will let the uterus involute over the cannula. Once the uterus decreases in size and becomes hard, cannula can be moved to-and-fro to completely evacuate the uterus.
(c) Its our practice to start Oxytocin 10 units/500 ml infusion once Suction cannula has been introduced after cervical dilatation. This decreases the blood loss and risk of perforation. Oxytocin infusion is continued for few hours after evacuation and if there is significant uterine bleeding other oxytocics such as ergometrine can be used. However, RCOG guidelines do not recommend the routine use of oxytocin before the completion of evacuation for the risk of trophoblastic embolization.
(d) Role of sharp curettage is unclear. This may increase the risk of uterine perforation and risk of uterine synechiae. Tissue is sent for histopatholgy.

Management After Evacuation

(a) Serial SpO_2 monitoring is done in patients with uterine enlargement greater than 14 weeks size as Pulmonary complications are observed at the time of molar evacuation in more than 20% of cases as compared to smaller uteri where the incidence of pulmonary complications is less than 1%. (4 reference). Respiratory distress occurs due of trophoblastic embolization, fluid overload, severe Anemia, preeclampsia or thyrotoxicosis.
(b) Anti D is given to Rh-negative women after evacuation because the Rh factor is expressed by the trophoblast.
(c) **Repeat evacuation** may be required in cases of heavy or persistent vaginal bleeding causing acute haemodynamic compromise, particularly in the presence of retained pregnancy tissue on ultrasound.

Q2: Is There any Role of Hysterectomy in Management of H Mole?

Hysterectomy may be considered in women older than age 40 years who have completed the childbearing. It provides permanent sterilization and decreases the need for subsequent chemotherapy by eliminating the risk of local myometrial invasion as a cause of persistent disease.

Induction of labor and hysterotomy are not recommended for molar evacuation, since, these methods increase maternal morbidity and the development of post molar GTN requiring chemotherapy.

Q3: How Will You Follow Her Up?

After complete hydatiform mole (CHM) 15–20% cases may develop GTN while risk is less (1–5%) after partial mole [2]. Serial quantitative serum hCG monitoring should be performed after molar evacuation. For monitoring patients with GTD, an hCG assay that can detect all forms of hCG (Free beta, N linked-free beta, C-terminal hCG, beta core and hyperglycosylated hCG) is required because these neoplasms often secrete abnormal forms of hCG.

Serum hCG levels should be obtained within 48 h of molar evacuation and followed every 1–2 weeks. For complete molar pregnancy, if hCG has reverted to normal within 56 days (8 weeks) of the pregnancy event then follow-up should be for 6 months from the date of uterine evacuation [2].

If hCG has not reverted to normal within 56 days of the pregnancy event then follow-up should be for 6 months from normalisation of the hCG level [2].

Q4: Is There any Role of Prophylactic Chemotherapy

Prophylactic administration of either methotrexate or actinomycin D chemotherapy at the time of or immediately following molar evacuation is associated with a reduction in the incidence of postmolar GTN to 3–8%. However, prophylactic chemotherapy may increase drug resistance and is associated with toxicities. it should be limited to situations in which the risk of postmolar GTN is much greater than normal and adequate hCG follow-up is not possible i.e. age more than 40 years, pre-evacuation hCG > 10^5 miu/ml, excessive uterine enlargement or theca lutein cysts larger than 6 cm [3].

Q5: What Is the Risk of Recurrence in Next Pregnancy and When To Plan and How To Manage Next Pregnancy?

The risk of recurrence is 0.6–2% after one molar pregnancy. The risk of repetitive molar pregnancies increases substantially if a woman has had two or more prior moles [4]. Mutations in *NLRP7 and KHCDC3L* have been reported in 50% of patients with recurrent molar pregnancy and in these cases molar tissue arises from zygote having biparental karyotype as compared to usual complete molar pregnancy where zygote karyotype is from paternal origin only. In such cases assisted reproduction with donor oocytes is recommended.

Woman should not conceive till the hCG surveillance is complete. Oral hormonal contraception (progestin-only or combined estrogen-progestin) or barrier methods can be safely used. OCPs do not increase the risk for or clinical aggressiveness of GTN when adjusted for risk factors. An intrauterine device (IUD) is not recommended in patients with persistently elevated hCG levels because of theoretical risk for perforation, infection, and hemorrhage. An IUD may be used in patients with confirmed GTD with undetectable or decreasing hCG levels.

All future pregnancies should be evaluated by a first-trimester obstetric ultrasound examination to rule out molar pregnancy. Women who have not received chemotherapy no longer need to have hCG measured after any subsequent pregnancy event.

Q6: How to Manage Twin Pregnancy with One Mole (CMF-Coexistent Mole and Fetus)

It is a rare situation developing in only 1 per 22,000 to 100,000 pregnancies [5]. The diagnosis is usually made on ultrasound. Although there is a high risk of spontaneous abortion, about 40–60% result in live births. Patients should be advised of the potential risks, including: (1) severe complications such as preeclampsia, hemorrhage, and thyrotoxicosis, which typically develop in the second trimester; (2) preterm delivery; and/or (3) GTN. The risk of GTN in such cases ranges from 27% to 46% [6].

In the absence of complications and normal genetic and ultrasound findings; pregnancy can be continued. For the woman who has decided to terminate the pregnancy suction evacuation under USG guidance is done, however, if the size of the fetal parts is big for the use of suction curettage, medical methods can be used.

Q7: Do All Pregnancies Need hCG Follow Up To Detect GTN?

The hCG surveillance is mandatory in CHM and partial HM. In PHM one to two weekly hCG is done till it is normal and monthly thereafter till two levels are normal.

In cases of abortions, if the fetal parts have been seen either on USG or at time of abortion, there is no need to send the products for histopathology and hCG surveillance. However, in cases of medical abortion or miscarriage where products of conception have not been seen or pathologically examined, beta hCG levels should be done 3 weeks after the event.

Any woman who has persistent or develops vaginal bleeding 8 weeks after pregnancy event, should be evaluated by hCG to rule out GTN.

Case 2 Low Risk GTN

Age, Parity, PS	27 years P2A1; ECOG = 1, BMI 24 kg/m^2
Presenting complaints	Persistent vaginal bleeding following a molar evacuation 3 months back Pre-evacuation BhCG: 1,51,000 U/ml
Examination	Uterus bulky, soft, anteverted, mobile bilateral fornices were free.
Co morbidities	Nil
Transvaginal sonography	USG: Uterine size 12 × 10 × 4.3 cm with increased vascularity in anterior myometrium bilateral ovaries normal
Weekly Beta HCG on follow up	B hCG: 28,270 mIU/ml, 26,720 mIU/ml, 27,840mIU/ml
Investigations	Hb: 13 g%, platelet count: 1,80,000/μl liver and kidney function tests: Normal
Radiological investigations	X-ray chest - normal CT abdomen – No evidence of metastasis CT head- Normal

Q1: Differential Diagnosis and Further Investigations Required for Management

This is a follow up case of previous CHM evacuated 3 months back who has been detected to have persistent high hCG values within ±10% during 3 weeks duration. This high hCG suggests persistent active trophoblastic tissue resulting in Post molar GTN. Commonly post molar GTN is because of invasive moles due to the extension of molar tissue in the myometrium. Even choriocarcinoma can develop following molar pregnancy in 2–3% of the cases [7]. Diagnosis of GTN is made by persistently elevated or rising levels of hCG. Histopathological confirmation is not required for diagnosing postmolar GTN before starting treatment. In the present case, diagnosis of postmolar GTN is suggested as per revised FIGO/WHO criteria (Table 27.1) of persistent elevated hCG values. High hCG values at the time of molar evacuation (>100,000 IU/L) seen in this case is one of the high-risk factors for development of GTN.

The differential diagnosis for the current case can be a new conception resulting in elevated hCG values and thus posing a diagnostic challenge. As there is no history of contraception in this cases, new pregnancy (which may be normal, ectopic or miscarriage) as a cause of high hCG needs to be ruled out by doing Ultrasound examination. (Transvaginal sonography is preferred as uterus is small).

Table 27.1 FIGO/WHO criteria for diagnosis of Post Molar GTN [5]

• Four persistently elevated weekly hCG values (± 10%) over 3 weeks period
• Three rising values of weekly hCG ≥10% over 2 weeks period
• Choriocarcinoma diagnosed on histopathology
• Detection of metastasis on clinical or radiological evidence

In this case on ultrasound there is no evidence of intrauterine or ectopic pregnancy. Rather presence of a vascular mass in the myo metrium of uterus is suggestive of invasive molar tissue. Thus, the diagnosis is Post molar GTN.

Q2: How Will You Further Investigate this Case?

For post molar GTN (likely invasive mole) further workup is required to screen for metastasis as metastasis commonly to vagina and lungs can occur in 15% of the invasive moles [7]. Therefore primary work up after diagnosis of GTN post molar involves complete physical examination including vaginal examination for vaginal metastasis, pelvic ultrasound with doppler and imaging for metastasis.

Pelvic USG doppler is done to rule out pregnancy and also to measure size of the disease, and estimate tumor volume and invasion.

For metastatic work up, we will do plain X ray chest as lungs are the commonest site of metastasis. As recommended by FIGO and NCCN [7], if x ray chest is normal, there no need of CT chest. If still CT chest is done with normal X ray findings, micrometastasis can be detected in 40% of the cases. But they have no bearing on prognosis and survival and only X ray chest is recommended for risk scoring [8]. Also it may unnecessarily increase the use of multiagent chemotherapy. If lung metastasis are detected on plain x ray, then further metastatic work up should include CT whole abdomen and pelvis and MRI brain.

Extensive workup for metastasis including CT chest and abdomen and MRI of head and pelvis is required only if choriocarcinoma is suspected which is unlikely in our case.

We will do other baseline laboratory investigations including complete blood counts, renal and liver function tests and thyroid function tests to assess stability and tolerability for chemotherapy.

Q3: How Will You Manage this Case?

As GTN is a chemo sensitive tumor, we will manage this case with primary chemotherapy. For selection of appropriate chemotherapy whether single or multidrug, the FIGO staging and scoring using prognostic scoring systems will be done to predict the response to single drug chemotherapy and risk of progression. FIGO staging is based on the extent and spread of the disease (Table 27.2).

Also prognostic score is given using WHO prognostic scoring system (Table 27.3) that considers 8 high risk factors including clinical, imaging and hCG levels that predict the development of resistance to single agent chemotherapy. Composite score has been found to be more predictive of response to chemotherapy as compared to individual factors.

FIGO stage 1 and II/III with prognostic score < 7 is considered low risk disease with almost 100% cure rate. They have low risk of resistance to single agent chemotherapy.

Accordingly this case of post molar GTN has FIGO Stage I and modified WHO prognostic score of 4 (Stage I:4). The primary treatment for this patient will be single agent chemotherapy using either methotrexate or Dactinomycin (Actinomycin D) in any of the recommended regimen (Table 27.4). At our institution we are using Methotrexate 8 day regimen alternating with Folinic acid as primary agent for low risk GTN as its better tolerated. The remission rates with this regimen are 74–93% [10].

Table 27.2 FIGO staging [9]

FIGO Stage	Description
Stage I	Disease limited to the uterus
Stage II	Spread of disease outside the uterus to genital structures like adenexa, vagina and broad ligament
Stage III	Lung metastasis (genital tract extension may or may not be there)
Stage IV	Distant metastasis (other than lungs, pelvis or vagina)

Table 27.3 FIGO/modified WHO prognostic scoring system [10]

Risk factor	0	1	2	4
Age	**<40 years**	≥ 40 years	–	–
Antecedent Pregnancy	**Molar preg**	Abortion	Birth	–
Interval from pregnancy to treatment (months)	**<4**	4 to <7	7 to <13	≥13
Serum hCG IU/L (before treatment)	$< 10^3$	10^3 to $<10^4$	**10^4 to $< 10^5$**	$\geq 10^5$
Largest tumor size including uterus(cm)	<3	3 to <5	**≥5**	
Site of metastasis	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastasis	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Multidrug

Table 27.4 Single agent chemotherapy regimens recommended for Low risk GTN [10]

Drug	Dosage[a]
Methotrexate	8 day regimen Inj methotrexate 1–1.5 mg/kg I/M 4 doses on alternate days, alternating with folinic acid oral 15 mg
	5 day regimen Inj methotrexate 0.4 mg/kg daily I/V or I/M for 5 days
Dactinomycin	Pulse regimen Dactinomycin 1.25 mg/m^2 I/V
	5 day regimen 0.5 mg fixed dose or 10–12 μg/kg I/V daily for 5 days

[a]The dosages are for single cycle, to be repeated every 2 weeks

Weekly I/M and Pulse dose I/V infusion Methotrexate regimens are no longer recommended due to lower efficacy.

Both the drugs are equally effective with remission rates of 75–90% with rare serious toxicities. Cochrane review in 2016 found evidence that Dactinomycin had higher cure rate in low risk disease as compared to Methotrexate [11]. However, 55% of this data included trials using weekly I/M Methotrexate regimen which is no longer recommended. In some studies multiday regimens methotrexate has been found to have higher remission rates as compared to Dactinomycin [7]. Due to better tolerance, Methotrexate in a multiday (5 or 8 days regimen) is usually primary chemotherapy for low risk disease and Dactinomycin is used as second line for resistance or toxicity.

Q4: How To Follow Up this Case After Start of Methotrexate Chemotherapy?

During treatment monitoring is done by two weekly hCG assays done at the start of each treatment cycle. Once the normal levels are achieved, further consolidation therapy is given with same chemotherapy cycle on which normal levels are achieved. NCCN guidelines recommend 2–3 cycles of chemotherapy after hCG normalization so as to decrease the risk of recurrence. Remission is defined after 3 normal values are achieved. After that monthly assays are recommended for 1 year. Risk of recurrence after low risk GTN treatment is <5%. For all GTN most of the recurrences (>70%) occur in first year and after that risk is <1% every year [12].

Q5: Is There any Indication of Starting Primary Combination Chemotherapy for Low Risk Disease?

Amongst low risk GTN, cases with prognostic score 5 and 6 have higher rate of resistance to the single agent chemotherapy, but still 30–60% remission can be achieved on single agent chemotherapy. Starting multiagent chemotherapy as primary treatment in all cases with high score of 5 or 6 is not justified as it will unnecessarily expose them to toxicities. Ultimately all patients who are started initially on single agent get treated. Various criteria have been proposed to identify the selective patients amongst this group who are at higher risk of being resistant to single agent chemotherapy thus candidates for multiagent primary chemotherapy, but none have been validated. Criteria suggested are uterine pulsatility index <1, metastatic disease, histopathologically diagnosed choriocarcinoma, very high hCG levels >4,00,000 IU/L. wherein combination of factors are present, primary multiagent chemotherapy may be considered in this category of intermediate risk group [13].

Q6: What Are the Indications for Change of Therapy?

Change of chemotherapy is required if there is inadequate response/ resistance to methotrexate or if due to toxicity like mucositis or other reactions optimal dosage can't be given. As this is low risk GTN without metastasis, still the risk of primary resistance is around 10–30% [14]. Chemotherapy resistance is detected on hCG surveillance when levels decrease <10% over 3 treatment cycles (plateau) or rise >10% over 2 consecutive cycles [7]. Whenever resistance occurs warranting change of therapy, restaging of the disease should be done.

If resistance is detected by hCG plateau after initial response and hCG levels are not very high (<1000 IU/L), we change to the alternative single agent i.e. Dactinomycin. In such scenario Dactinomycin achieves complete response in around 75% cases [15].

Hysterectomy can also be considered as disease is limited to the uterus and if the woman doesn't desire future fertility.

Q7: When Will You Switch Over to Multiagent Chemotherapy in Low Risk GTN?

In cases where initial response to single agent is good but later there is rapid rise of hCG to high values or if there is poor response to single agent therapy, multiagent chemotherapy is preferred as second line treatment. The hCG threshold above which multiagent therapy as second line is preferred has been revised over time. NCCN guidelines recommend multiagent chemotherapy (EMA-CO regimen as for high risk disease) if hCG levels rapidly rise to ≥1000 IU/L during treatment with single agent chemotherapy. Repeat workup to check for metastasis is required. Cure rate with EMA-CO approaches 100% even with relapse/ resistant low risk disease [7].

Patients with higher prognostic risk score (5 or 6) are at higher risk of resistance to monotherapy. In a study only 30% of these cases attained remission on second line monotherapy [16]. Multiagent chemotherapy should be preferred in such cases.

Q8: How To Follow Up on Second Line Therapy? Is It Different from Primary Therapy FU?

Follow up is done in the same way as in primary therapy with 2 weekly hCG levels, but action is taken earlier if the levels rise or plateau. NCCN guidelines recommend additional treatment if hCG levels plateau over 2 treatment cycles or rise over 1 cycle. Patient is to be reassessed for metastasis and change to multiagent EMA-CO regimen is done. If patient is already on EMA-CO, further treatment is done as per high risk cases (discussed in Case 3).

Q9: Is There any Role of Surgery for Managing Low Risk GTN?

In chemoresistant disease confined to the uterus, hysterectomy can be performed if fertility is no longer desired. Isolated resistant metastatic disease can also be surgically removed.

Surgery is also needed if there is disease related hemorrhage and embolization has failed or not available.

Q10: Is There any Role of Repeat D&C in Managing Such Cases?

In post molar GTN if disease is limited to the uterus, D&C can be considered as an alternative to chemotherapy in low risk disease. In properly selected cases with low hCG levels, 40% cases may have remission without any chemotherapy [17]. But cases with high score of 5 or 6 or high hCG levels ≥1500 IU/L are more likely to still require chemotherapy. In the present case, as disease is in the myometrium and not in the cavity, and also hCG levels are high, so there is no role of D&C.

Case 3 High Risk GTN

Age, Parity, PS	25 years P1A1; ECOG = 1, BMI of 18.3 kg/m^2
Presenting complaints	Irregular bleeding per vaginum for 7 months; following previous history of D&C for spontaneous abortion of 8 weeks gestation; histopathology not available
Examination	Moderate pallor, uterus enlarged to 8 weeks gravid uterus size, soft, anteverted, mobile bilateral fornices were free
Co morbidities	Nil
Transvaginal sonography	Echogenic shadows 3 cm size, (multiple trabeculae) with increased vascularity. Myometrium was very thinned out at fundus of the uterus. Bilateral ovaries were normal
Beta HCG	9,73,776mIU/ml
Investigations	CBC-hemoglobin 8 g%, TLC- 6000/cc, DLC-, platelets KFT, LFT, INR normal
Radiological investigations	X-ray chest - multiple cannon ball shadows CT abdomen – No evidence of metastasis

Q1: How Will You Manage this Case?

Presence of irregular vaginal bleeding in reproductive age group demands urine pregnancy test and ultrasound to rule out pregnancy related event. In present case, UPT was positive and USG revealed absence of gestational sac in uterus or adnexa and findings were suggestive of extremely vascular mass invading the myometrium raising the suspicion of GTN. Serum beta hCG levels confirmed it to be GTN and serum beta hCG levels more than one lakh with such an USG picture suggests the diagnosis of choriocarcinoma. She does not need histology for confirmation and D&C in such a case can be catastrophic due to massive haemorrhage.

Q2: How Will You Further Investigate this Patient and What Is the Stage and Prognostic Score of this Patient?

She needs full metastatic work up for staging and scoring. In presence of lung metastasis, CT of Abdomen and pelvis and CT/MRI brain is required to rule out brain metastasis (BM). As a general rule, brain MRI with or without intravenous gadolinium contrast is the gold standard for the assessment of BMs and shows a better sensitivity over contrast-enhanced CT for metastasis located in the posterior fossa where bone artifact can hide small metastases. In cases of strong suspicion of BM and negative imaging, CSF hCG levels can be done with simultaneous plasma levels. Plasma to CSF hCG ratio less than 60 indicates brain metastasis [18].

In absence of brain metastasis she becomes FIGO stage **III:7. i.e high risk stage III GTN.**

(FIGO score- Age-0; Antecedent pregnancy-1; Interval months from index pregnancy-1; pretreatment hCG levels-4; Largest tumor size including uterus-1; others-0)

Q3: What Are Treatment Options for Her? How Many Cycles of Chemotherapy Are Recommended?

After correcting her anemia with target hemoglobin of at least 10 g%, multiagent chemotherapy should be given in dedicated GTD centre or by medical oncologist with enough experience in dealing with GTN. EMA-CO regimen is treatment of choice and includes combination of etoposide, methotrexate, dactinomycin/cyclophosphamide and vincristine (Table 27.5). Cycle is repeated every 2 weeks until hCG normalizes and continued for 3 more cycles as consolidation therapy. Before each treatment (day 1): CBC, beta hCG, serum electrolytes, creatinine, Alkaline phosphatase, ALT, GGT, LDH, bilirubin and before (day 8) repeat CBC are done.

Other multiagent regimens have also been used but there are no RCTs and EMA/CO is preferred because of its efficacy and acceptable toxicity.

Q4: What Is the Efficacy and Complications of EMACO Regimen?

Efficacy of EMACO in curing high risk GTN ranges from 54–91% [19] and remission can be seen after 3–6 cycles. There can be initial failure to treatment or who have responded to EMA/CO may show plateauing of low hCG values. The recurrence rate in high risk GTN is reported around 20% requiring salvage therapy [20]. EMA/CO has acceptable toxicity. Common side effects of nausea, vomiting are dealt with antiemetic protocols. Bone marrow depression resulting in anemia, thrombocytopenia and neutropenia is dealt with blood transfusion and G-CSF to prevent the treatment delays. In our practice it is not a routine to give G-CSF in EMA-CO regimen, however in EMA-EP cycle injection Filgrastim 300 mg SC is given from day 9–14 of each treatment cycle.

Secondary tumours, including leukemia, colon cancer, melanoma and breast cancer have been reported with chemotherapy for GTN. These have been attributed to cumulative doses of etoposide and appear in patients after 5 years who have received a total dose of 2 g/m^2 of etoposide.

Q5: Will Treatment Differ if There Is Brain or Liver Metastasis?

Cerebral metastasis is less common in post molar GTN, however, 20% of patients with choriocarcinoma have CNS involvement. Management of brain metastasis is complex and requires multidisciplinary approach. These patients may require emergency measures to combat intracranial bleeding or raised intracranial pressure. The dose of the methotrexate infusion is increased in EMA/

Table 27.5 EMA/CO regimen

Day 1	Dose	route	Remarks
Etoposide	100 mg/m^2	IV infusion 45–95 minutes	Filgrastim, 300mcg SC on days 9–14 may be required for prophylaxis of neutropenic fever, or prevention of treatment delay
Dactinomycine	0.5 mg	IV push	
Methotrexate	300 mg	IV infusion over 12 h	
Day 2			
Etoposide	100 mg/m^2	IV infusion 45–95 mintes	
Dactinomycine	0.5 mg	IV push	
Leucovorin (Folinic acid)	15 mg 12 h × 4 doses	PO, start 24 h after start of day 1 methotrexate infusion	
Day 8			
Vincristine	0.8 mg/m^2	IV in 50 ml ns over 10 min	
Cyclophosphamide	600 mg/m^2	IV in 250–500 ml 0ver 30 min	

CO protocol to 1000 mg/m^2 along with leucovorin dose to 30 mg every 12 h for 3 days starting 32 h after the infusion with or without intrathecal methotrexate. In addition to chemotherapy, whole brain irradiation (3000 cGy in 200 cGy daily fractions), stereotactic radiosurgery, and or craniotomy with surgical excision may be required depending on the symptoms, number, size and location of the brain lesions. Cure rates of 50–80% have been reported [7].

Patients of liver metastasis will require multimodality therapy including chemotherapy with embolization of metastasis or surgical resection of isolated metastasis or targeted radiotherapy.

Q6: How Will You Manage Ultrahigh Risk GTN?

Patients with prognostic score of 13 or more are ultrahigh risk. In presence of liver. Brain or extensive metastasis cases do poorly with first line multiagent chemotherapy. EP/EMA or other more dose intensive regimens yield better results than EMA/CO. Starting with recommended dose of multiagent regimens in these patients results in sudden tumour lysis with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure resulting in early mortality within 4 weeks. To avoid this initial low dose induction chemotherapy with etoposide 100/m^2 IV and cisplatin 20 mg/m^2 IV on Days 1 and 2, every 7 days for 1–3 courses prior to EMA/CO or EP/EMA is recommended [7].

Q7: When and How Will You Use Salvage Therapy?

Patients failing EMA/CO therapy or having relapse should be re-evaluated and given revised stage and scoring. Multimodality treatment with surgical intervention to remove isolated metastasis of resistant cells can be helpful. Such cases are mostly salvaged with EP/EMA or TP/TE. In non-responders high dose chemo (HDC) regimens can be tried along with autologous bone marrow or stem cell transplant but is associated with high toxicity and infertility. Recently Programmed death ligand 1 (PDL 1) has been identified in all GTN lesions and use of pembrolizumab (anti-PD-1) has shown promising results in resistant and relapse cases. This drug induced complete responses in 75–80% of unresectable, chemo-resistant GTN including cases that had failed HDC [21]. The patients who failed to respond were shown to lack lymphocytic infiltration of tumour. A phase II trial of avelumab in low-risk GTN who were resistant to single agent chemo showed 53% complete remission with one patient having successful pregnancy [22]. Immunotherapy in GTN is still evolving and clinical trials are investigating its use as a single drug or in combination with chemotherapy for GTN (Table 27.6).

Q8: At End of Treatment if Low Levels of b hCG Persist with no Clinical Evidence of Disease, What Should Be the Next Step in Management?

This is most likely a quiescent GTN and occurs when a small focus of syncytiotrophoblast cells remain which are slow-growing producing small amounts of hCG. This does not progress to invasive disease as long as the cytotrophoblast, or intermediate cells, are absent. These syncytiotrophoblast cells do not respond to chemotherapy as they are extremely slow-growing and do not

Table 27.6 Salvage Therapy in High Risk GTN

• EMA/EP (EMA is same as in EMA/CO, however on day 8 etoposide 100 mg/m^2 is given along with cisplatin 75 mg/m^2)
• TP/TE (paclitaxel, cisplatin/paclitaxel etoposide repeated every 2 weeks)
• MBE (methotrexate, bleomycin, etoposide)
• VIP or IEC (ifosfamide, etoposide, cisplatin or carboplatin) 3 weekly
• FA (5 FU, actinomycin D)
• FAEV (floxuridine, actinomycin D, etoposide, vincristine)
• High dose chemotherapy with autologous bone marrow or stem cell transplant
• Immunotherapy with pembrolizumab

result in normalization of hCG. Hypergylcosylated hCG (hCG-H) is produced by cytotrophoblast cells and is associated with trophoblast invasion, growth of cytotrophoblast cells, and is the main form of hCG produced in active choriocarcinoma and gestational trophoblastic neoplasm. f hCG-H (hCG-H/total hCG) is a sensitive marker for distinguishing active GTN from quiescent GTD. Majority of patients with hCG-H less than 27% of total hCG will not progress. However, patients of quiescent GTN should be monitored closely as one fourth of patients will exhibit rising total hCG levels and hCG-H and convert to malignant disease.

In this clinical situation the possibility of phantom hcg or pituitary hcg should also be kept in mind. A phantom hcg is due to heterophilic antibodies in serum which are detected by seum assays used for hcG test and are not secreted in urine because of large molecular size. It can be ruled out by Urine test for hCG which will be negative, or serial dilution of the serum sample, as false hCG levels will remain largely unaffected by dilution, or use of different commercial assays that will often result in a significant fluctuation in the hCG level.

Pituitary beta hCG – This false positive can be found due to raised levels of luteinizing hormone due to lack of feed back inhibition by gonadal hormones which have been knocked out by the gaonadal toxicity of chemotherapy. In the case of pituitary hCG, the production can be inhibited with oral contraceptive pills or using LHRH antagonist.

Q9: Indications for Hysterectomy for High-Risk GTN?

Hysterectomy does not have much role in high-risk GTN. Emergency hysterectomy may be called for in perforating choriocarcinoma resulting in hemoperitoneum and in few cases of chemoresistant tumours if uterus is the only site of residual tumour, hysterectomy can be considered.

Q10: What Is the Follow Up Protocol After Completion of Treatment and What Contraceptive Choices She Has and When Should She Plan Her Next Pregnancy?

After treatment is over and hCG levels are normal, patients of GTN should be monitored with serial determination of serum hCG levels at 2 weeks interval for first 3 months and then at monthly intervals for at least 12 months. The risk of recurrence after 1 year of remission is less than 1% and is higher for high risk GTN. Therefore patients with high risk GTN should be monitored for another year with hcg at 6 months and 12 months.

Oral contraceptives are recommended during chemotherapy and follow up in remission period. She can plan pregnancy after the follow up protocol is complete. Early ultrasound is recommended in subsequent pregnancy as risk of molar pregnancy is 1–2%. There is no risk of increased congenital anomalies. Patient should have histological evaluation of placenta and postdelivery hCG levels.

Effect of chemotherapy on ovarian function should be told to the patients. Single agent chemotherapy has minimal effect on ovarian function however, with EMA/CO at age 40 years the risk of menopause is 13% and at age 45 years 30% [2].

Women can undergo artificial reproductive techniques and hormonal stimulation for fertility treatment, however AMH is not a reliable indicator of ovarian reserve after chemotherapy. It is safe for women to have HRT.

Case 4 Placental Site Trophoblastic Tumor

Age, Parity, PS	44 years P1A1; ECOG = 0, BMI of 22 kg/m^2. Last abortion 4 years back
Presenting complaints	Spotting per vaginum for 10 days preceded by 4 month amenorrhea, urine pregnancy test positive
Examination	Uterus A/V 6 weeks soft, mass in right and anterior fornix 3 × 3 cm close to uterus, left fornix free
Co morbidities	Nil
Transvaginal sonography	Uterus bulky, ET = 9 mm, Rt adnexa solid echogenic lesion with cystic and solid component 3 × 2 cm close to uterus, Lt. adnexa normal, no free fluid
Beta HCG	10,737 mIU/ml
Investigations	CBC-hemoglobin 8gm%, TLC- 6000/cc, platelets: 1,56,000 KFT, LFT, INR normal X-ray chest - normal
With a provisional diagnosis of ectopic pregnancy received Inj methotrexate 1 mg/ kg, vitals monitoring D4 β hCG: 12,000 mIU/ml, D7 β hCG: 3693 mIU/ml, D12: β hCG: 5090 mIU/ml	
CECT abdomen + pelvis ***(in view of rising HCG* placenta site trophoblastic tumor**)	Dilated tortuous vascular channels with contrast filling in arterial phase noted in anterior myometrium extending to right adnexa with prominent right fallopian tube. Rest of the uterus is normal, cervix normal, left adnexa normal Upper abdomen normal
Surgery, intraoperative findings	Underwent TAH + RSO + left salpingectomy Uterus anterior bulge +, increased vascularity B/l tubes and ovaries normal On cut section: Small 1 × 1 cm vascular growth present at right cornua and upper part of right lateral wall
Histopathology	Placental site trophoblastic tumor. Tumor site fundus 1.5 × 1 × 1 cm. Microscopic tumor extension confined to uterus. Margins – closest distance of malignant tumor free margin 1 cm. No lymphovascular invasion. No mitosis, no fetal tissue. Fallopian tube normal. Proliferative endometrium, chronic cervicitis

Post surgery B hCG: 1202 mIU/ml
Weekly titres: 991 mIU/ml, 891mIU/ml, 955mIU/ml
Patient received Methotrexate + Leucovorin + Actinomycin weekly × 3 cycles

Q1: What Is the Differential Diagnosis of Above Case?

Depending upon history, examination and ultrasound findings, she fits into criteria of ectopic gestation, however possibility of germ cell tumour of ovary should have been kept as adnexal mass showed solid areas. The uterus was empty on ultrasound, Doppler ultrasound could have helped in knowing vascularity in myometrium and within the mass. May be extreme vascularity in myometrium on TVS Doppler could have picked up the lesion at first visit and diagnosed it as GTN.

Starting methotrexate was too early as patient was not fully evaluated.

Q2: What Are the Peculiar Features of the PSTT

Peculiar Features of PSTT

- Arise from intervillous intermediate trophoblast cells, are slow growing and secrete low levels of hCG.
- Are diagnosed on histopathology and stain positive for HPL and Mel-CAM (CD 146).
- These can occur many years after pregnancy event. Clinical presentations include amenorrhoea, irregular bleeding, or are diagnosed on D&C/ hysterectomy specimen.
- Prognostic factors of FIGO scoring system do not apply to PSTT.
- These are not very chemo sensitive and have propensity for lymphatic spread.
- Rarely these may be associated with nephrotic syndrome or/and SLE like picture

Q3: What Are High Risk Factors for PSTT? Is this Patient Belonging To High-Risk Case/What Is the Risk Category of this Patient?

Age more than 40 years, interval between antecedent pregnancy and onset of symptoms more than 2 years, FIGO stage of the disease, large size of the tumor, deep myometrial invasion. Poor histological grade in terms of tumor necrosis, nuclear atypia and more than 5 mitotic figures/10 HPF are associated with poor prognosis. The two worse prognostic factors are interval of disease more than 48 months from index pregnancy and stage IV disease [7].

This patient is stage one and high risk because of age factor and more than 2 years interval between index pregnancy and GTN.

Q4: Current Management Strategies of PSTT? What Is the Role of Lymphadenectomy?

Surgical management (hysterectomy and excision of metastasis if feasible) is the best option and stage 1 low risk cases do not require adjuvant chemotherapy. Lymphatic metastasis is more common in PSTT as compared to choriocarcinoma. The pelvic lymph node metastasis in stage I - PSTT is estimated to be 5–15% [7]. Therefore pelvic lymph node sampling/lymphadenectomy should be considered especially for patients with large, deeply invasive tumours and stage II-IV disease.

Adjuvant chemotherapy is required for patients with high risk factors and Stage II-IV. Multiagent platinum-based chemotherapy is advisable as PSTT respond poorly to single agent chemotherapy.

The present case had persistent raised beta hCG levels after surgery. She has been put on MA combination regimen and beta hCG levels are showing plateauing indicating no response/drug resistance. She demands thorough search for metastasis by imaging and in this case PET-CT should be done. Isolated metastasis can be surgically removed followed by EP/EMA or other regimens along with G-CSF. Although PSTT do not fully express PDL-1, immunotherapy with pembrolizumab has shown good results in chemo resistant cases.

Q5: Is There any Role of Conservative Surgery?

As most women with PSTT are young, fertility preservation is desirable in many cases. In these cases resection of the tumour mass can be done by abdominal, laparoscopic or hysteroscopic methods. Most of the cases finally require hysterectomy if the tumour has not been completely removed. Stage 1 disease without high risk prognostic features like deep invasion, necrosis, high mitosis etc. may be considered for conservative surgery if fertility is strongly desired.

Q6: How Will You Follow Up this Case?

The hCG is not a reliable indicator for PSTT, hence it has to be supplemented with imaging for follow up. PET/CT or MRI at the end of chemotherapy and then every 6 months for 2–3 years and annually thereafter at least for 5 years is recommended.

Key Points

- GTD includes benign but potentially malignant molar pregnancies and neoplastic entities including Invasive mole, Choriocarcinoma, PSTT, ETT and Atypical Placental Nodule
- GTN can develop following any pregnancy event.
- Suction evacuation is the method of choice for managing Molar pregnancy irrespective of the uterine size.
- Follow up with hCG after molar evacuation is required as risk of developing GTN after complete mole is 15–20% and after partial mole, it is less 1–5%.

- GTN can be diagnosed clinically and histopathological confirmation is not required before starting treatment.
- Low risk cases (Score < 7)are primarily managed with Single agent Chemotherapy with Methotrexate or Dactinomycin
- High risk (Score ≥ 7) are managed primarily with multiagent chemotherapy with EMA-CO
- Cycles are repeated every 2 weeks till hCG levels normalize. Further 2–3 cycles are given as consolidation chemotherapy. Remission is defined after 3 normal hCG values.
- If hCG values plateau or rise during treatment, it suggests resistance and warrants change of therapy.
- Reassessment for staging and prognostic scoring is required every time the therapy is changed.
- All cases of low risk GTN if properly managed, can achieve 100% remission.
- Most of the recurrences occur in first year, therefore monthly HCG monitoring is recommended for 1 year after remission in GTN
- Contraception preferably with combined oral contraceptive pills is recommended during chemotherapy and follow up protocol.
- Intermediate Trophoblastic Neoplasia (PSTT/ETT) are not so chemo sensitive, therefore surgery (hysterectomy) is the mainstay of treatment
- hCG not being a reliable marker for PSTT/ETT, it is supplemented with imaging during follow up

References

1. Kaur B, Short D, Fisher RA, Savage PM, Seckl MJ, Sebire NJ. Atypical placental site nodule (APSN) and association with malignant gestational trophoblastic disease; a clinicopathologic study of 21 cases. Int J Gynecol Pathol. 2015;34:152–8.
2. Tidy J, Seckl M, Hancock BW, on behalf of the Royal College of Obstetricians and Gynaecologists. Management of gestational trophoblastic disease. BJOG. 2021;128:e1–e27.
3. Wang Q, Fu J, Hu L, et al. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2017;9(9):CD007289.
4. Sebire NJ, Fisher RA, Foskett M, Rees H, Seckl MJ, Newlands ES. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. BJOG. 2003;110:22–6.
5. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. FIGO cancer report 2018. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynecol Obstet. 2018;(143):79–85.
6. Ngan HYS, Seckl MJ, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynecol Obstet. 2018;143(Suppl. 2):79–85.
7. National Comprehensive Cancer Network(2022) Gestational Trophoblastic Neoplasia (version 1.2022 – October 06, 2021). https://www.nccn.org/professionals/physician_gls/pdf/gtn.pdf Accessed May 25,2022.
8. Frijstein MM, Lok CAR, van Trommel NE, ten Kate-Booij MJ, Massuger LFAG. Lung metastases in low-risk gestational trophoblastic neoplasia: a retrospective cohort study. BJOG. 2020;127(3):389–95.
9. Gestational trophoblastic neoplasms (female reproductive organs). In: Amin MB, editor. AJCC cancer staging manual, 8th ed. Chicago: Springer; 2017.
10. Horowitz NS, et al. Epidemiology, diagnosis, and treatment of gestational trophoblastic disease: a Society of Gynecologic Oncology evidenced-based review and recommendation. Gynecol Oncol. 2021;163:605–13.
11. Lawrie TA, Alazzam M, Tidy J, Hancock BW, Osborne R. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2016;2016(6):CD007102.
12. Balachandran K, Salawu A, Ghorani E, Kaur B, Sebire NJ, Short D, Harvey R, et al. When to stop human chorionic gonadotrophin (hCG) surveillance after treatment with chemotherapy for gestational trophoblastic neoplasia (GTN): a national analysis on over 4,000 patients. Gynecol Oncol. 2019;155(1):8–12.
13. Braga A, Paiva G, Ghorani E, Freitas F, Velande GGC, Kour B, Unsworth N, Lozano-Kuehne J, dos Santos Esteves AV, FilhoJ R, Amim J, Aguiar X, Sarwar N, Elias KM, Horowitz NS, Berkowtiz RS, Seckl MJ. Predictors for single-agent resistance in FIGO score 5 or 6 gestational trophoblastic neoplasia: a multicenter retrospective cohort study. Lancet Oncol. 2021;22:1188–98.
14. Maestá I, Nitecki R, Horowitz NS, et al. Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: the New England Trophoblastic Disease Center experience. Gynecol Oncol. 2018;148:161–7.
15. Prouvot C, Golfier F, Massardier J, et al. Efficacy and safety of second-line 5-day Dactinomycin in case of methotrexate failure for gestational trophoblastic neoplasia. Int J Gynecol Cancer. 2018;28:1038–44.

16. Sita-Lumsden A, Short D, Lindsay I, Sebire NJ, Adjogatse D, Seckl MJ, Savage PM. Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at Charing cross hospital, 2000-2009. Br J Cancer. 2012;107(11):1810–4.
17. Osborne RJ, Filiaci VL, Schink JC, Mannel RS, Behbackht K, et al. Second curettage for low -risk nonmetastatic gestational trophoblastic neoplasia. Obstet Gynecol. 2016;128(3):535–42.
18. Bakri Y, al-Hawashim N, Berkowitz R. CSF/serum beta-hCG ratio in patients with brain metastases of gestational trophoblastic tumor. J Reprod Med. 2000;45:94–6.
19. Deng L, Zhang J, Wu T, Lawrie TA. Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. Cochrane Database Syst Rev. 2013;(1): CD005196.
20. Anantharaju AA, Pallavi VR, Bafna UD, Rathod PS, Vijay CR, Shobha K, et al. Role of salvage therapy in chemo resistant or recurrent high-risk gestational trophoblastic neoplasm. Int J Gynecol Cancer. 2019;29(3):547–53.
21. James C, Susanna S, Michael JS. Treatment of gestational trophoblastic diseases in 2020s. Curr Opin Obstet Gynecol. 2021;33(1):7–12.
22. You B, Bolze PA, Lotz JP, et al. Avelumab in patients with gestational trophoblastic tumors with resistance to single-agent chemotherapy: cohort A of the TROPHIMMUN phase II trial. J Clin Oncol. 2020;38:3129–37.

Cervical Cancer in Pregnancy

28

Felicia Buruiana and Ashwini Bilagi

Introduction

It is widely recognised that the cervical screening programme in the UK contributed to a significant decrease in the incidence of invasive cervical cancer (CC) in young women. Nevertheless, CC is the most common type of gynaecological cancer in pregnancy, with an incidence estimated between 0.8–1.5 cases per 100,000 births [1, 2]. Almost two-thirds of CC are diagnosed during the first two trimester, and usually up to stage IB1 [3].

To date, there are no established guidelines for the treatment of CC in pregnancy, due to the rarity of the disease and the lack of randomised control studies. As a consequence, the management of CC follows the guidelines for the non-pregnant woman with cervical cancer. It is recognised that the prognosis is not influenced by pregnancy [4].

The treatment decision is challenging because it involves both mother and fetus; it must be taken in a multidisciplinary context, involving the obstetrician, the gynaecologist oncologist, radiologist, pathologist and paediatrician. The treatment should be individualised taking into account the stage of the disease, lymph node status, histologic type, the gestational age, imaging assessment, desire for fertility preservation and patient's wishes.

Case 1: Cervical Cancer in Pregnancy: First Trimester

Age, Parity, PS	32-year-old, G6P5, previous one cesarean section 10 weeks POG, ECOG = 0, BMI: 43
Clinical presentation	Presented to emergency with abnormal vaginal bleeding and passage of clots Pelvic examination: 1–2 cm cervical mass in the anterior lip of cervix. The cervix was mobile and bilateral parametria were free Clinical stage 1B1
Co morbidities	Depression and anxiety, history of gastric banding 2 years ago
Transvaginal sonography	Single live fetus 11 weeks POG, liquor adequate
Cervical biopsy	Keratinizing squamous cell cancer cervix
MRI	1.5 cm heterogeneous mass showing areas of intermediate and high signal intensity in cervix. No parametrial invasion. No enlarged pelvic or Para aortic nodes. Bilateral ovaries normal

F. Buruiana (✉)
Pan Birmingham Gynaecology Oncology Centre, Birmingham, UK
e-mail: f.buruiana@nhs.net

A. Bilagi
Birmingham City Hospital, Sandwell and West Birmingham Hospitals, Birmingham, UK
e-mail: a.bilagi@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_28

Surgery	Mifepristone was given 36 h before hysterectomy for termination of pregnancy Radical hysterectomy, bilateral salpingectomy with ovarian conservation and bilateral lymph nodes dissection at 11 weeks of pregnancy
Histology	Keratinizing squamous cell cancer stage 1B1, tumor size 1.8 × 1.5 cm, presence of lympho-vascular space invasion and outer third of cervical stroma involvement, lymph nodes negative

Q: What Investigative Work Up Should Be Done in These Cases?

In this case since there was a visible growth and a biopsy was done to confirm the diagnosis. Endocervical curettage is not recommended in pregnancy. The risk of severe bleeding on a cervical biopsy is only 1–3%.

In case there is no visible growth colposcopy is performed in the following situations [5]:

1. Vaginal bleeding or contact bleeding excluding obstetric factors;
2. Obvious abnormalities in the cervix noted during gynecological examination;
3. Lesions suspicious of being an invasive cancer;
4. Cervical cytology screening which meet the criteria of referral colposcopy:
   (a) Atypical squamous cells of undetermined significance (ASC-H).
   (b) Low grade squamous intraepithelial lesion (LSIL).
   (c) High-grade squamous intraepithelial lesion cannot be excluded;
   (d) High-grade squamous intraepithelial lesions (HSIL) and atypical glandular cells (AGC).

Colposcopy is challenging in pregnancy due to pregnancy related physiological changes that make interpretation challenging. These changes include stromal edema, increased vascularity and hyperplasia of glandular cells. It is better to be undertaken within the first and second trimesters of pregnancy. If early colposcopy is not satisfactory, it can be repeated after 20 weeks of pregnancy.

In case of suspicion on colposcopy, doing a flat LLETZ is better than cold knife conisation as the latter is associated with increased risk of bleeding [6]. **Conization** is usually postponed to the postpartum period, however it should be performed if there is suspected invasion. A short cone is taken because the procedure has a diagnostic role rather than therapeutic, endocervix should not be manipulated to prevent premature rupture of membranes and also the location of the lesions in pregnant women is predominantly in the ectocervix [7]. The most frequent complications are haemorrhage (5% in the first and second trimesters and 10% in the third), miscarriage (25%), preterm labour (12%) and infection (2%). The risks of miscarriage and bleeding are considerably reduced when conization is performed during the second trimester, preferentially between the 14th and 20th weeks [8, 9].

Once the diagnosis of invasive cancer is confirmed, ultrasound and magnetic resonance imaging (MRI) are the imaging modalities of choice for preoperative staging. Few prospective studies concluded that transrectal and transvaginal USS is comparable with the diagnostic accuracy of MRI [10, 11]. MRI determines the tumour size in the three dimensions, stromal invasion, vaginal and parametrial invasion, and lymph node involvement [12]. There is no clear conclusion about the adverse effects of the MRI on the fetus in any trimester [13]. However, some studies do not recommend it in the first trimester due to lack of evidence [14]. Even if no adverse effects to the neonates have been demonstrated in any of the three trimesters, the consensus is for Gadolinium to be used only if absolutely necessary [15]. MRI findings of cervical cancer in pregnancy are comparable with the non-pregnant status. The patient in our case also underwent MRI investigation, which allowed a tailored treatment planning.

Q: What Are the Challenges Seen in Pregnancy with Respect to Cytology in Pregnancy?

The main challenges are related to the pregnancy induced changes mainly determined by the levels of maternal oestrogen and progesterone. They lead to glandular hyperplasia of cervical mucosa, migration of squamous-columnar junction, active proliferation of basal cells, irregular cell morphology, and enlargement of nuclei, which are easily misdiagnosed as highly squamous intraepithelial lesions or even invasive cancer [16].

In view of the described changes, it is recommended that cervical cytology smears should be interpreted by experienced pathologists in order to reduce misdiagnosis.

Q: Describe the Treatment of Histological LSIL and HSIL in Pregnancy

The management of LSIL and HSIL histology is as follows [17, 18]:

1. Cervical histology of LSIL (CIN1 grade) inpregnancy can be postponed to 6 weeks postpartum forreview.
2. Cervical histology of HSIL (CIN2 and 3 grade)in pregnancy should be reviewed every 12 weeks after excluding invasive cervical cancer; cervical cytology and colposcopy should be re-evaluated at 6 weeks postpartum.
3. If re-examination indicates that the disease progressed to suspicious invasive cancer, a repeated biopsy should be taken.
4. If highly suspected of cervical invasive cancer, cervical loop electrosurgical excision (LEEP) or cervical coldknife conization (CKC) can be performed to make a definite diagnosis.

Pregnancy rarely accelerates the progress of cervical intraepithelial lesions. Approximately 64% of all grades of CIN regress or remain stable in pregnancy, postpartum progression is noted only in a small number of cases [19]. Most importantly, the preferred mode of delivery should be vaginal, caesarean section is indicated only in case of obstetric reasons.

Q: What Is the Effect of Pregnancy on Cervical Cancer and What Additional Problems Do We Anticipate in the Management of These Cases?

It has not been proven that the pregnancy accelerates the natural history of cervical cancer. The disease-specific survival is independent of the trimester of pregnancy when the diagnosis is made. If the diagnosis is made before 16 weeks, immediate treatment should be applied. If the diagnosis is made later, expectant management for fetal maturity can be applied [20].

Certainly, the antenatal and postnatal progresses in recent years with the administration of steroids and artificial surfactants for neonates have contributed to a huge difference in the survival of preterm babies, making an early delivery, after 24 weeks, a potential outcome.

Q: Comment of the Safety of Conization in Pregnancy?

Conization is performed, on very rare occasions, that too in second trimester,for diagnostic purposes in pregnancy, and not for therapeutic purposes because there is a high risk of bleeding, miscarriage, preterm birth, but also because of increased risk of residual disease (up to 50%) [21]. Therefore, conisation should only be performed in pregnancy if there is microinvasive carcinoma on biopsy, or persistent cytological findings of invasive carcinoma in the absence of colposcopic or histological confirmation of disease [6, 22].

Radical trachelectomy in pregnancy either vaginal, abdominal or laparoscopic is not

recommended due to high rate of obstetric and surgical complications.

Q: Briefly Describe the Management of Cervical Cancer Diagnosed Before 22 Weeks

1. **Stage 1A1 (depth of invasion (DOI) less than 3 mm) without LVSI**- pregnancy can be maintained, and treatment started after delivery. It can be closely followed up treated postpartum [5]. In these cases, a colposcopy and ultrasound/ MRI should be performed every 6–8 weeks to assess the disease course. Alternatively, a cone biopsy can be performed between 14–20 weeks and women can aim for vaginal birth in absence of obstetric contraindications [1]. The rate of lymph node metastasis is 0.6%. In case the patient is not desirous of fertility, termination followed by definite treatment can be done as in this case.
2. **For cervical cancer stages IA1 with LVSI, IA2 and above**, surgery including radical hysterectomy with bilateral lymphadenectomy is the treatment of choice. Women may be counselled and should be also given the option of termination of pregnancy and definitive treatment in same sitting if she has completed her family. Size of the lesion and the gestation are important considerations before treatment planning.

   In case the patient is desirous of continuing pregnancy, It is recommended that tumor involvemnet of suspicious nodes should be done for risk stratification. Laparoscopic lyphadenectomy is carried out uptil 20–22 weeks to ascertain if nodes are negative or positive as the latter may prevent the adoption of a pregnancy safe strategy. Nodal resection beyond 22 weeks is usually not advisable due to large uterine size, number of nodes retrieved and risks of surgery. Sentinel lymph node (SLN) biopsy is possible in pregnancy, and the location of the SLN is a good indication for choosing this treatment plan [23]. However, there is insufficient data to recommend in pregnancy.

3. **For stage IA2-IB1, with negative lymph nodes** less than 1% of the patients had parametrial extension. Therefore, conization or simple trachelectomy may be considered as treatment options [24]. Simple trachelectomy is a less complex operation with removal of tumour 1 cm from tumour boundary [25]. The patient should be counselled regarding the associated risks of haemorrhage and premature delivery. Cervical length monitoring can be done by serial ultrasound scans. The pregnancy is allowed to progress, and the completion of treatment is delayed after the delivery. Radical trachelectomy is not recommended in pregnancy due to increased risk of bleeding and prolonged operating time, approximately 3.5 h [26].
4. **For stages IA2-IB1 and positive lymph nodes -**termination of pregnancy is recommended, followed by standard treatment for cervical cancer.
5. **For patients with stage IB2-IIAand above-**termination of pregnancy is recommended followed by definitive treatment. NACT can be recommended, if the patient wishes to continue the pregnancy and provided lymph nodes are negative. NACT can be used until the fetus is mature and delivered, followed by standardised treatment for cervical cancer [27].
6. **Stage 1B3, IIA2 and above:** NACT can be given if close to term, followed by termination once fetal maturity is obtained and definite treatment may includes chemoradiation. In exceptional circumstances surgery can be done in 1B3 if the tumor has decreased in size; but only after discussion in MDT and careful counselling.

Case 1: She was referred for adjuvant chemoradiotherapy, which she is currently receiving, with no major side effects.
At annual follow up, she had recovered well, with no complaints, and no evidence of recurrence on the MRI scan.

Case 2: Cervical Cancer in Pregnancy: Second Trimester

Age, Parity, PS	28-yearG4P3L3, previous vaginal deliveries, 19 + 5 weeks POG, ECOG = 0
Clinical presentation	C/O constant left-sided abdominal pain radiating down to her leg and intermittent vaginal spotting Speculum examination: 4 × 4 cm irregular, exophytic cervical growth Vaginal and rectal examination: 4 × 5 cm growth on cervix with free right fornix. Scarring in the left fornix, and early left parametrial invasion could not be excluded on clinical grounds only
Co morbidities	Anxiety and asthma, chronic smoker
Cervical biopsy	Moderately differentiated squamous cell carcinoma cervix
MRI	5.4 cm maximal dimension lesion involving the whole of the cervix with left parametrial extension. There was no vaginal or uterine involvement and no lymphadenopathy FIGO stage IIB
PET scan	FDG uptake in the known cervical lesion but no extra- pelvic disease
Management	Following MDT discussion, she underwent laparotomy, hysterotomy and delivery of the fetus at 21 weeks of gestation. The proposed treatment after the surgery was radical chemo radiation 50.4 Gy in 28 fractions alongside weekly cisplatin, followed by 3 sessions of intrauterine brachytherapy which she is currently receiving

Q: Discuss Management Beyond 22 Weeks of Pregnancy and Role of Neoadjuvant Chemotherapy in Cervical Cancer

NACT is an option in the management of the cervical cancer in pregnancy when definitive treatment needs to be delayed until the fetus maturity or in locally advanced tumours. Based on the available evidence, it controls the disease and prevents the tumour from progressing until delivery [28].

Chemotherapy is contraindicated during the first trimester because of the increased risk in

miscarriage and fetal malformation, however it can be administered in second and third trimester under the following circumstances [29, 30]:

1. In node-negative stage IB1, with tumour size <2 cm: NACT is given to patients wishing to preserve pregnancy during the second trimester.
2. In stage IB2 (2–4 cm): NACT can be given either to node-negative patients as before or after nodal assessment by lymphadenectomy.
3. In stages IB2 – IIB: NACT is used until maturity and delivery. This will be followed by chemoradiation

Cisplatin, a platinum-based drug, is the most used in pregnancy (50–100 mg/m^2), alone or in combination with paclitaxel (175 mg/m^2) [15]. The administration is once every 3 weeks. Other alternative regiments have been reported using Cisplatin 75 mg/m^2 with Ifosfamide 2 g/m^2 every 2 weeks [29]. Chemotherapy is not recommended beyond 35 weeks of gestation in order to reduce the risk of spontaneous labour occurring when a patient becomes neutropenic. Three weeks interval is recommended between the final dose and caesarean section as this allows time for maternal and fetal bone marrow recovery [31].

Attention needs to be paid and thorough counselling of the patient is required because during pregnancy, multiple changes in physiology occur affecting the drug bioavailability. This may have therapeutic and toxic results for both pregnant woman and fetus.

Chemotherapy can act directly, or indirectly (by affecting placenta) on fetal growth [32]. After the fetal organs are developed, chemotherapy can still affect fetal eyes, genitals, hematopoietic system, and central nervous system [32]. It can also supress maternal and fetal bone marrow, causing anaemia, thus leading to fetal growth restriction [33].

Reported fetal effects after chemotherapy treatment in pregnancy are: intrauterine growth restriction, prematurity, and low birth weight, hearing loss and myelosuppression.

Case-3 Cervical Cancer in Pregnancy: Third Trimester

Age, PS	31 years, G3 P2 + 0,previous two vaginal deliveries ECOG −1, BMI 25
Clinical presentation	33 weeks of pregnancy C/O: Three episodes of unprovoked vaginal bleeding and discharge Backache × 3 months **Speculum examination:** Exophytic growth on cervix 3 × 4 cm
Co morbidities	Nil
Cervical biopsy	Poorly differentiated non keratinising squamous cell cancer cervix
MRI pelvis	Heterogenous enchancing area on posterior lip of cervix measuring 3.5 × 2.8 × 1.5 cm with no vaginal or parametrial extension. No retroperitoneal lymphadenopathy
Surgery	Delivery by elective caesarean section at 36/40, with steroids given for fetal lung maturation, followed immediately by radical hysterectomy bilateral salpingectomy and bilateral pelvic lymphadenectomy

Q: Which Investigations Are Required to Aid Management

Women found to have any suspicious cervical lesion in pregnancy should be urgently referred to colposcopy via a 2 week wait pathway. They should be seen by an experienced Gynaecologist or Colposcopist as colposcopy during pregnancy requires a high level of skill due to the physiological changes of pregnancy (increased cervical mucus, gland prominence, cervical hyperaemia, eversion of the columnar epithelium) making cervical assessment more challenging. If during Colposcopy invasive disease is suspected, adequate biopsy is crucial in making the diagnosis. In pregnancy, punch biopsy carries an increased risk of bleeding (25%) with consideration given to performing the procedure in theatre with appropriate facilities to manage haemorrhage. It should be noted that a punch biopsy identifying only CIN does not exclude invasion reliably [34].

The first line investigation for staging cervical cancer in pregnancy is MRI. It is considered safe at any gestation as it does not involve ionising

radiation. However, pregnancy can cause difficulties in the interpretation of the MRI images due to the physiological changes being misinterpreted. This can include fetal movements leading to a reduction in image quality, as well as dilated pelvic veins mistaken for pelvic adenopathy. Contrast is often not essential in the staging of cervical cancer but if it is required, gadolinium- and iodine-containing should be avoided as they cross the placenta.

Although CT is often contraindicated in pregnancy, its benefit may outweigh risk if full staging is required such as if lung or pleural spread is highly suspected. It should be considered as second line to MRI. If CT is required, efforts should be made to reduce the radiation exposure to the fetus such as with the use of an abdominal shield and liaison with radiologist to facilitate low dose radiation where possible [35].

The presence of hydronephrosis can be assessed using ultrasound. It is considered safe in pregnancy for both the mother and fetus. Importantly, physiological hydronephrosis can be observed in 90% of pregnancies. This is due to the ureters being compressed by the gravid uterus as well as the relaxation effect of progesterone on smooth muscle.

Chest x-ray could be considered if lung metastases are suspected. It carries minimal risk to the fetus due to the low dose of ionising radiation. In light of this, the British Thoracic Society recommends performing chest radiographs for the same indications as in non-pregnant women.

Although considered at earlier gestations, laparoscopic lymphadenectomy is technically difficult to perform and not recommend after 22 weeks' gestation. This is due to the size of the gravid uterus, the insufficient number of nodes retrieved and the risks of surgery.

What Is the Further Management?

This is a case of IB1 cervical cancer for which the gold standard of care in non pregnant patient is radical hysterectomy and bilateral salpingectomy with ovarian conservation in squamous cell cancer but oophorectomy may be considered in adenocarcinoma of cervix as have higher risk of metastasis to ovaries than squamous cell cervical cancer. Bilateral pelvic lymphadenectomy is performed as it may not be feasible to peform sentinel nodes with the presence of gravid uterus. This treatment would also be offered in cases of IA1 with lymphovascular space invasion (LVSI) and IB2 cervical cancer.

Plans should be made with the involvement of the multidisciplinary team which should include Gynaecological Oncological Surgeon, an Obstetrician with an interest in Fetal-Maternal Medicine, Neonatologist, Medical and Radiation Oncologist, Pathologist, Radiologist, Midwife, Cancer Specialist Nurse, and Psychologist. There are no standardised procedures for the treatment of cervical cancer in pregnancy. Care should be individualised and made in discussion with the woman with her wishes taken into account [1, 31].

Owing to this woman's relatively advanced gestation, delivery should be considered in order to facilitate treatment. The impact of the mode of delivery on oncological outcomes is controversial. In light of this, all modes of delivery should be discussed. The risks of vaginal birth can include postpartum haemorrhage (with significant blood loss), the tumour obstructing the birth canal as well as the higher risk of recurrence at the site of episiotomy compared to abdominal wall in incisions. For these reasons caesarean section (classical caesarean section) is generally considered the safer mode of delivery [36].

Caesarean-radical hysterectomy can be performed in women with early stage cervical cancer without radiological evidence of lymph node metastasis or extra-pelvic disease. Caesarean-radical hysterectomy carries additional risks compared with radical hysterectomy alone, namely haemorrhage. The blood loss is commonly attributable to high vascularity of the pelvic organs and increased length of surgery as requires careful dissection of parametrium, ureteric dissection and pelvic lymphadenectomy.

The surgery should be performed in a tertiary centre by a gynaecological oncologist with an obstetrician. One should aim for a classical caesarean section to avoid extension of tears in

the cervix which is soft, vascular and friable because of presence of tumour. Careful hemostasis should be maintained throughout. If profuse bleeding, can consider internal iliac artery ligation if ligation of uterine vessels at origin does not sufficiently curtail the haemorrhage. Careful assessment of parametrium and vaginal cuff is essential as the anatomy is altered with an expanded parametrium because of the gravid uterus. Because of the additional surgical risks, some surgeons offer to delay hysterectomy until 4–6 weeks postnatal which is not a recommended practice as it causes progression of cervical cancer and impacts outcome. However, performing a combined caesarean section with radical hysterectomy, as in this case, avoids the need for a second laparotomy. Although rare, recurrence within the abdominal wall has also been described. The placenta should be sent for histology to assess for metastases. Corticosteroids to aid fetal lung maturation should be considered pre-operatively if the surgery is performed under 36 weeks gestation.

Q: What Is the Prognosis?

Many women present with early stage cervical cancer in pregnancy. During pregnancy, the oncological outcome of cervical cancer is similar to that of the non-pregnant population, although the impact of pregnancy on the tumour itself remains unclear.

Key Points

- Cervical cancer in pregnancy has to be managed by a multidisciplinary approach in a tertiary care cancer centre, taking into consideration both maternal and fetal factors
- The treatment should be individualised depending on the gestational age, disease stage, histological type, lymph nodes status, patient's wishes whether to continue the pregnancy
- Clinical presentation of cervical cancer in pregnancy can be easily confused with pregnancy changes and may be difficult to diagnose
- Pelvic lymphadenectomy should be considered before 22 weeks of pregnancy to decide further treatment, when there are suspicious nodes.
- Neoadjuvant chemotherapy can be considered in pregnancy to delay treatment till fetal maturity.
- Radical hysterectomy can be performed with caesarean section for early stage cervical cancer in third trimester after fetal maturity. For locally advanced stage cervical cancer chemoradiotherapy after the caesarean delivery is considered.

References

1. Smith LH, Dalrymple JL, Leiserowitz GS, Danielsen B, Gilbert WM. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. Am J Obstet Gynecol. 2001;184:1504.
2. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol. 2003;189:1128.
3. China S, et al. Management of gynaecological cancer in pregnancy. TOG. 2017;19:139–46.
4. Liu H, et al. Small cell carcinoma of thre cervix at 32-week gestation: a case report and review of the literature. Lab Med. 2014;45(1):52–5.
5. Beharee N, Shi Z, Wu D, Wang J. Diagnosis and treatment of cervical cancer in pregnant women. Cancer Med. 2019;8:5425–30.
6. Halaska MJ, Drochytek V, Shmakov RG, Amant F. Fertility sparing treatment in cervical cancer management in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2021;75:101–12.
7. Palle C, Bangsbøll S, Andreasson B. Cervical intraepithelial neoplasia in pregnancy. Acta Obstet Gynecol Scand. 2000;79(4):306–10.
8. Vlahos G, Rodolakis A, Diakomanolis E, et al. Conservative management of cervical intraepithelial neoplasia (CIN(2-3)) in pregnant women. Gynecol Obstet Invest. 2002;54(2):78–81.
9. Douvier S, Filipuzzi L, Sagot P. Prise en charge d'une néoplasie intra-épithéliale du col de l'utérus en cours de grossesse [Management of cervical intra-epithelial neoplasm during pregnancy]. Gynecol Obstet Fertil. 2003;31(10):851–5.
10. Epstein E, Testa A, Gaurilcikas A, Di L, Ameye L, Atstupenaite V, et al. Early-stage cervical cancer: tumor delineation by magnetic resonance imaging and

ultrasound - a European multicenter trial. Gynecol Oncol. 2013;128:449–53.
11. Fischerova D, Cibula D, Stenhova H, Vondrichova H, Calda P, Zikan M, et al. Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer. Int J Gynecol Cancer. 2008;18:766–72.
12. Nicolet V, Carignan L, Bourdon F, Prosmanne O. MR imaging of cervical carcinoma: a practical staging approach. Radiographics. 2000;20:1539–49.
13. Kanal E, Barkovich A, Bell C, Borgstede J, Bradley W Jr, Froelich J, et al. ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol. 2007;188:1447–74.
14. Nagayama M, Watanabe Y, Okumura A, Amoh Y, Nakashita S, Dodo Y. Fast MR imaging in obstetrics. Radiographics. 2002;22(3):563–80; discussion 580-2.
15. Han SN, et al. Cervical cancer in pregnant women: treat, wait or interrupt? Assessment of current clinical guidelines, innovations and controversies. Ther Adv Med Oncol. 2013;5(4):211–9.
16. Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. Lancet. 2012;379(9815):558–69.
17. Creasman WT. Cancer and pregnancy. Ann N Y Acad Sci. 2001;943:281.
18. Ferris DG, Cox JT, O'Connor DM, Wright VC, Foerster J. Colposcopy in pregnancy in Modern Colposcopy Textbook and Atlas. 2nd ed. ASCCP, Kendall/Hunt Publishing Company; 2004. p. 350–92.
19. Lihui W, Yun Z, Xing X, et al. Expert consensus on the management of cervical cancer in pregnancy. Chin J Obstetr Gynecol. 2018;19(2):190–2.
20. Germann N, Haie-Meder C, Morice P, et al. Managementandclinicaloutcomesofpregnant patients with invasive cervical cancer. Ann Oncol. 2005;16(3):397–402.
21. Demeter A, Sziler I, Csapo Z, Szantho A, Papp Z. Outcome of pregnancies after cold-knife conization of the uterine cervix during pregnancy. Eur J Gynecol Oncol. 2002;23:207–10.
22. Howe T, Lankester K, Kelly T, Watkins K, Kaushik S. Cervical cancer and pregnancy: diagnosis, staging and treatment. Obstet Gynaecol. 2022;24:31–9.
23. Silva LB, Silva-Filho AL, Traiman P, et al. Sentinel node mapping in a pregnant woman with cervical cancer: a case report. Int J Gynecol Cancer. 2006;16(3):1454–7.
24. Botha MH, Rajaram S, Karunaratne K. Cancer in pregnancy. Int J Gynecol Obstet. 2018;143:137–42.
25. Rob L, Skapa P, Robova H. Fertility-sparing surgery in patients with cervical cancer. Lancet Oncol. 2011;12(2):192–200.
26. Căpîlna ME, Szabo B, Becsi J, Ioanid N, Moldovan B. Radical trachelectomy performed during pregnancy: a review of the literature. Int J Gynecol Cancer. 2016;26(4):758–62.
27. Halaska MJ, Scasso S. Cervical cancer. In: Textbook of cancer in pregnancy. European Socienty of Gynaecological Oncology; 2017.
28. Fruscio R, Villa A, Chiari S, Vergani P, Ceppi L, Dell'Orto F, et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol. 2012;126(2):192–7.
29. Amant F, Halaska MJ, Fumagalli M, Dahl Steffensen K, Lok C, Van CK, et al. Gynecologic cancers in pregnancy guidelines of a second international consensus meeting on behalf of the ESGO task force "Cancer in Pregnancy". Int J Gynecol Cancer. 2014;24(3):394–403.
30. Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;121:337–43.
31. Howe T, Lankester K, Kelly T, Watkins R, Kaushik S. Cervical cancer in pregnancy: diagnosis, staging and treatment. TOG. 2022;24:31–9.
32. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004;5(5):283–91.
33. Kozuki N, Lee AC, Katz J, et al. Moderate to severe, but not mild, maternal anemia is associated with increased risk of small-for-gestational-age outcomes. J Nutr. 2012;142(2):358–62.
34. Reed N, Balega J, Barwick T, Buckley L, Burton K, Eminowicz G, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: recommendations for practice. Eur J Obstet Gynaecol. 2021;256:433–65.
35. Goméz Rodrigo S, Calderon J, Dionisi JN, Santi A, Mariconde JM, Rosato OD, et al. Cervical cancer in pregnancy at various gestational ages. Int J Gynecol Cancer. 2021;31:784–8.
36. Castellani C, Di Loreto E, Perugino G, Orsi M, Preti EP, Ramezzana IG, et al. Caearean hysterectomy for cervical cancer complicating pregnancy: Life-saving procedure or hazardous choice? J Gynecol Oncol. 2021;4(1):1049.

Part VII

Fertility Preservation in Gynaecological Cancers

29 Fertility Sparing in Cervical, Endometrial and Ovarian Cancer

Felicia Buruiana and Bindiya Gupta

Introduction

Preserving fertility becomes a big challenge in gynaecological cancers in adolescents and young adults. The 2012–2016 Surveillance, Epidemiology, and End Results (SEER) statistics report 36.5% of cervical cancers, 6.5% of uterine cancers, and 7% of ovarian cancers were diagnosed in women <45 years old [1].

Various medical and surgical options have been proposed to preserve fertility in these group of patients. The aim of conservative surgery is to preserve an organ's functionality and to avoid radical resection when possible.

The principles of fertility preservation are:

- Oncologists must be aware of situations where the treatment will affect fertility and must have a knowledge of options like conservative surgery, assisted reproductive technologies like embryo, oocyte or ovarian tissue cryopreservation, medical management of endometrial cancer etc. at the same time balancing fertility preservation with oncological safety.
- Delay of definitive treatment to achieve fertility goals i.e. completion treatment is invariably required
- Realistic patient factors of fertility potential (age, ovarian reserve, associated medical conditions, previous obstetric history)

This chapter is dedicated to the fertility sparing options for each type of gynaecological malignancy with a practical approach of the different aspects of managing the patient in the multidisciplinary context.

Case 1: Fertility Preservation in Cervical Cancer

Age, Parity, PS	34-year-old, Nulliparous, smoker ECOG = 0
Clinical presentation	Complaints: Vaginal discharge occasionally blood stained x 6 months Cervical smear: HSIL, high risk HPV positive Colposcopy: High grade lesion suggestive of invasion Procedure done: LEEP
Co morbidities	Nil
Histopathology	Well differentiated squamous cell carcinoma; 4.3 mm invasion depth on loop histology, stage 1A2, LVSI negative, margins positive for HSIL
MRI	No mass lesion in cervix, no parametrial invasion. No enlarged pelvic or Para aortic nodes. Bilateral ovaries normal (Fig. 29.1)

F. Buruiana (✉)
Pan Birmingham Gynaecology Oncology Centre, Birmingham, UK
e-mail: f.buruiana@nhs.net

B. Gupta
UCMS and GTB Hospital, New Delhi, India

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_29

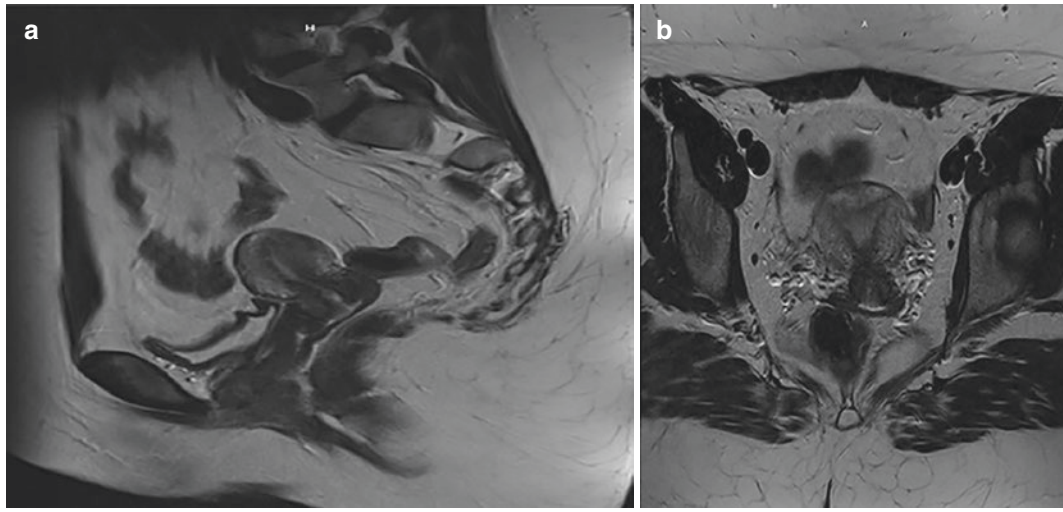


Fig. 29.1 (**a**, **b**) T2 weighted MRI image showing normal cervix and normal parametrium

Surgery	Conization was done as the LEEP margin was positive for HSIL
Histology	Moderately differentiated keratinizing squamous cell cancer stage, stage 1A2, no LVSI, margins negative

Q: What Are the Selection Criteria for Fertility Preservation

These can be classified as follows [2]:

Patient related factors:

- Desirous of fertility
- No contraindications e.g. multiple co-morbidities
- No other associated issues related to fertility potential

Disease related factors:

- Stage 1B1, size <2 cm
- Squamous cell cancer or adeno carcinoma (HPV associated)
- MRI showing tumor at least 1 cm away from internal os

The contraindications to fertility preservation are high Delgado score (tumor size, LVSI, deep stromal invasion), positive excision margins, nodal or parametrial spread, large tumor size (>4 cm) and aggressive histologies (in neuroendocrine, clear cell and non HPV Ca).

Q: What Are the Fertility Sparing Options in Cancer of the Cervix

A personalised strategy with a multi-disciplinary approach involving a gynecologic oncologist, medical and radiation oncologist with an infertility specialist is crucial.

There are various options of fertility saving procedures for patients with cervical cancer, in terms of surgical approach and extent of paracervical resection. For 1A/1A2 disease with no lymphovascular space invasion (LVSI), negative endocervical curetting after excision, and negative surgical margins, loop electrosurgical excision (LEEP) or cold knife conization (CKC) is sufficient. However, in patients with positive LVSI, the risk of recurrence may increase up to 9%; hence, an additional pelvic lymph node dissection and sentinel node mapping are recommended in those cases [3]. The five-year disease-free survival was 94% and overall survival rates were 97% in patients who underwent conization combined with pelvic node dissection via laparoscopy.

For 1B1 cervical tumours, radical trachelectomy can be performed vaginally (VRT) as well as abdominally (ART), both are safe and have similar

outcomes. Less radical procedures (i.e., deep cone and simple trachelectomy) for tumours less than 2 cm, with negative sentinel lymph nodes and other pelvic lymph nodes, are comparable with the results of VRT and ART. Lymph node evaluation must be done in these stages either by sentinel nodes or pelvic lymphadenectomy.

For tumours larger than 2 cm tradical trachelectomy is not usually not offered. In these situations, neoadjuvant chemotherapy is another option used mainly in trials, with promising results [4]. Pregnancy outcome varies statistically with the different methods. However, there is limited experience for offering trachelectomy for greater than 2 cm cervical cancers with an increased risk of recurrence (17%) that complicates the oncological safety of uterine preserving procedures in these cases [5]. In a systematic review, of twenty-three studies, one hundred and eighty patients out of 205 patients (87.8%) underwent fertility-sparing surgery. VRT was the most common surgery performed in 34.4%, pregnancy rates were 84.8% and global recurrence and death rates were 12.8% and 2.8%, respectively.

In advanced cases undergoing chemoradiation the strategies include oocyte cryopreservation, embryo cryopreservation and ovarian transposition. The latter has success rate of 88.6% for preservation of *ovarian function* and the success is limited due to altered blood flow and scattered radiation. Fixation of ovaries more than 1.5 cm above iliac crest is the most important factor for intact ovarian function [6]. Alternatively, high-precision modern radiation therapy methods such as MRI-guided *brachytherapy*, image modulated radiation therapy can be utilized to reduce the scattering effect of radiation and reduce the planned dose to non affected uterus to below 20–25 Gy [7].

Q: Discuss the Pregnancy Rates and Oncologic Outcomes After Fertility Sparing Surgery

In a recent systematic meta analysis out of 3044 women the clinical pregnancy rate was 55.4% of which 20% were ART assisted. The average clinical pregnancy rate was 65% after conization/simple trachelectomy and 53.6% after radical trachelectomy (67.5% after VRT versus 41.9% ART; p = 0.005) [8].

The main difference between ART and VRT techniques is the extent of resection of the parametria and disruption of pelvic autonomic innervation (inferior hypogastric plexus). Larger resection of the paracervix implies greater disruption of the uterus and tube innervation. Less extent of parametrial resection, preservation of uterine vascularisation and innervation along with keeping a cervical length of 1 cm improves pregnancy outcomes. The robotic approach is another surgical option however there is still not enough evidence in terms of pregnancy outcomes.

The overall recurrence rate after fertility sparing surgery is less than 4% and mortality rate is around 1 percent [9]. The recurrence rate and clinical death rate is higher around 8.5% and 2% after neoadjuvant chemotherapy [10]. Tumours larger than 2 cm have a worse oncological outcome and it is recommended that nodal assessment should be done before NACT.

Case 2: Fertility Preservation in Endometrial Cancer

Age, Parity, PS	35-year-old, Nulliparous, ECOG = 0, BMI: 34
Clinical presentation	Complaints: Trying to conceive for 3 years, Unexplained infertility getting evaluation Menstrual cycles regular, Normal flow Endometrial biopsy showed
Co morbidities	Nil
Histopathology (endometrial biopsy)	Atypical hyperplasia (AH)
MRI	No mass lesion in endometrium, endometrial thickness 14 mm, hyperechogenic (Fig. 29.2) Cervix, bilateral ovaries normal, no lymphadenopathy

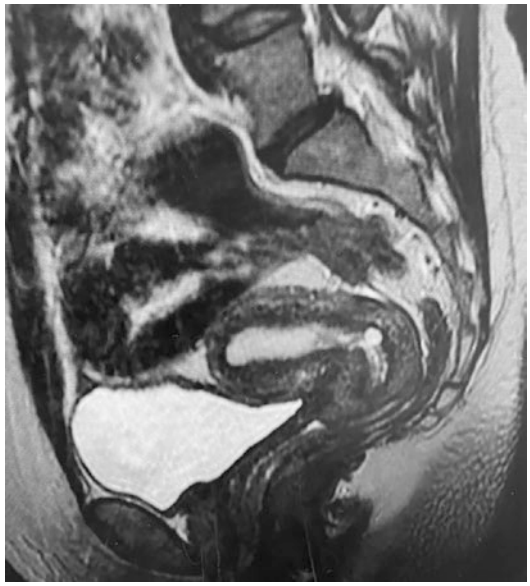


Fig. 29.2 T 2 weighted MRI image showing thickened endometrium 14 mm, no obvious growth and no myometrial invasion

Q: What Are the Risk Factors of Complex Atypical Hyperplasia (AH)/Endometrial Cancer (EC) in Premenopausal Women?

Endometrial cancer (EC) is rare in women less than 45 years old; it has an incidence of 1.2–24/100.000 in women between 25 and 49 years old [11]. A hyperestrogenic state is the major cause of atypical hyperplasia (AH) and it also leads to the development of type I oestrogen-dependent endometrial cancer (EC). Past medical history of infertility, unopposed use of conjugated oestrogens, obesity, increased endogenous oestrogen, genetic predisposition (Lynch syndrome), polycystic ovarian syndrome (PCOS) and anovulatoy cycles contribute strongly to the development of AH and EC.

Q: What Are the Selection Criteria for Fertility Preservation?

The selection criteria for fertility preservation in women diagnosed with EC are:

- Complex atypical hyperplasia/Grade 1 endometrioid adenocarcinoma
- Stage 1A, no myometrial invasion, no LVSI
- Desirous of fertility with no other associated issues related to fertility potential
- No contraindications e.g. multiple co-morbidities or any contraindication to medical treatment

Q: What Investigative Work Up Should Be Done in this Case?

The management of the early stage of EC is guided by the degree of myometrial invasion, deciding the suitability for conservative and fertility preservation treatment.

Ultrasound (transabdominal, transvaginal) is the first line imaging method, and it can describe the myometrial invasion in expert hands. Contrast MRI scan is the most reliable method in assessing the degree of myometrial invasion and tumor size. Nodal involvement can also be excluded on MRI.

Histology of the tissue, either by Pipelle or endometrial biopsy (D&C) at hysteroscopy complements the imaging findings and is compulsory in making the decision for fertility sparing treatment. High grade endometrioid and non endometrioid histology is a contraindication to fertility preservation. An expert histologic review is important as the tumor may be upgraded. In PORTEC -1 on expert slide review 24% patients had their grading altered in the final histology [12]. Molecular classification wherever available can be done on the biopsy report and POLE tumours are associated with better outcomes. Also MMR deficient tumours can be determined on immunohistochemistry and may be associated with Lynch syndrome in 10% cases.

All patients should be evaluated before and after the fertility-sparing treatment at a fertility clinic. These include factors related to ovarian reserve namely antral follicular count, serum anti mullerian hormone (AMH) levels, presence of co morbidities and husband factors like semen

analysis. These will help decide whether the patient can go for spontaneous conception or will need assisted reproduction.

Q: What Are the Available Management Options?

Detailed counselling is integral to management. The patient should be told that its not a standard treatment for endometrial cancer but is indicated for fertility preservation. The cure rate & risk of recurrence should be explained. The patient should be willing for close follow up, progestin use and 3 monthly FU after pregnancy. She should be told that there will be a need for further hysterectomy in case of failure of treatment/or after pregnancies. At least 6 months of treatment has to be given to ensure a good response rate.

There are a variety of management options including progestins, GnRH analogues, aromatase inhibitors, oral contraceptives, antioestrogens [13].

These include megestrol acetate (MA) (160–480 mg/day) per day and medroxypogesterone acetate (MPA) (400–600 mg/day) mg per day. The common side effects are weight gain, liver dysfunction, and abnormal blood coagulation tests [14]. The contraindications to progestin based therapy includes breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis and smoking.

Levonorgestrel intrauterine system (LNG-IUS) is another progestin option which is widely used. Use of oral progestins has also been tried in combination with GnRH, tamoxifen. Treatment with levonorgestrel intrauterine device in combination with oral progestins with or without gonadotropin-releasing hormone analogs can also be considered.

Hysteroscopic resection of the pathologic area followed by oral progestins is another alternative.

Q: What Is the Surveillance Protocol?

To assess response, endometrial biopsy (with or without hysteroscopy) and imaging at 3–4 and 6 months must be performed. If no response is achieved after 6 months, standard surgical treatment is recommended. It is desirable to try pregnancy in the first month itself after treatment response. Continuous hormonal treatment should be considered in responders who wish to delay pregnancy. Strict surveillance is recommended every 6 months with clinical history with acknowledgment of any changes in signs and symptoms, physical examination and transvaginal sonography. During follow-up, hysteroscopic and endometrial biopsy should be performed only in case of abnormal uterine bleeding or abnormal ultrasound findings.

Q: What Is the Safety of Ovulation Induction in Women Previously Treated for EC?

Ovulation induction does not appear to be associated with increased risk of relapse, and subsequent pregnancies do not worsen oncological outcomes. There is no clear optimal duration, protocol or number of attempts for ovarian stimulation in women with early-stage EC.

Q: Role of Completion Surgery?

Fertility preserving treatment, or non-surgical treatment, is not the standard management of the EC, hence once family is complete, a completion surgery is required. The definite treatment for early-stage EC is total hysterectomy (laparoscopic usually, or abdominal) with bilateral salpingectomy +/−oophorectomy. Women less than 45 years with low grade endometrioid endometrial cancer, stage 1, myometrial invasion <50%, no genetic factors and no ovarian mass on gross imaging may be given an option of ovarian preservation.

The patient should be counselled in detail about the procedure, and its role in the management of early-stage EC. Long-term recurrences have been described in literature, and completion surgery is the way to avoid them.

Q: Role of Fertility Preserving Treatment in Patients with Lynch Syndrome

Lynch syndrome (also known as the hereditary non-polyposis colorectal cancer) is an autosomal dominantly inherited cancer syndrome characterised by the development of colorectal, endometrial, and ovarian cancers and various other neoplasia frequently diagnosed at an early age. It is caused by pathogenic variants of the DNA mismatch repair system genes MLH1, MSH2, MSH6, and PMS2, which prevent the correction of acquired errors during DNA synthesis [15]. Efficacy of fertility sparing hormonal treatment remains debatable. In fact, it should be noted that the molecular mechanisms causing disease in patients with Lynch syndrome differ from those occurring in sporadic cases [16]. Therefore, progestin therapy, which is more commonly used in the latter group, may be ineffective in patients harboring a defect in mismatch repair genes. Accordingly, in the guidelines and expert consensuses discussing fertility sparing treatment for atypical hyperplasia and endometrial cancer in Lynch syndrome patients, this issue is still debated and the safety of fertility sparing treatment in Lynch syndrome patients remains unclear, if not unproven. After the patient has completed her family, risk reducing surgery should be advised.

Q: What Are the Oncologic and Fertility Outcomes After Conservative Management of Endometrial Cancer

Gallos et al. (2012) in a systematic meta analysis reported a regression rate of 77%, 40.6% relapse rate and 28% live birth rate in complex hyperplasia with atypia. In Endometrial cancer the regression rate was 85.6%, relapse rate was 26% and LBR was 26.3% [17].

In another recent metanalysis (2022) the regression rate was 79.7%, relapse rate 35.3% with 26.7% pregnancies and 20.5% live birth rate [18]. The highest chances of live birth were in women 35 years or younger (30.7%), combination of progestins with hysteroscopic resection (30.7%), or at least 3 years of follow-up (42.4%).

She was given levonorgestrel intrauterine system (LNG IUS) and advised life style modification. Repeat endometrial biopsy 6 months later showed persistence of CAH with grade 1 endometrial cancer, which was MMR proficient. MRI at this stage confirmed endometrial growth in lower part of uterus of 1.5 cm with no myometrial invasion. As patient progressed on LNG IUS, option of hysterectomy was discussed which the patient declined and patient was started on oral megesterol acetate along with LNG IUS.
MRI and endometrial biopsy repeated in 6/12 months. MRI showed regression of previously noted endometrial lesion. EB showed progesterone effect with mild atypia.
Treatment unchanged for 6 months and MRI and endometrial biopsy was repeated which showed no evidence of any precancer or cancerous lesion in uterus. Patient is now being considered for IVF.

Case 3: Fertility Preservation in Borderline Ovarian Tumours

Age, Parity, PS	32 years, P1 + 0 ECOG = 0, BMI:25
Clinical presentation	Keen on conception **Symptoms:** Abdominal pain, distension, urinary frequency **Examination:** Abdominal mass 16 weeks' size
Co morbidities	Nil
Ultrasound	**Ultrasound:** Bilateral complex ovarian masses; left side 10x8 cm; right side 6 × 8 cm
Tumour markers	CA125: 32 KU/L, CA19–9: 78KU/L, CEA: 5 µg/L, BHCG, AFP negative
Surgery	Laparoscopic bilateral ovarian cystectomy
Histology	Bilateral borderline mucinous tumours with focal microinvasion in one ovary with surface involvement, FIGO stage 1C2

Q: Describe Fertility Sparing Surgery, Oncologic and Pregnancy Outcomes for Borderline Tumours (BOT) both Unilateral and Bilateral?

In young patients who have not completed child bearing, fertility sparing surgery should be done. For disease limited to one ovary, either ovarian cystectomy or unilateral salpingo-oophorectomy is appropriate if no ovarian tissue is identified for preservation. Ovarian cystectomy is usually performed in stage IA disease with no surface ovarian involvement. In bilateral ovarian masses, type of surgery performed depends on clinical presentation and may vary from unilateral adenexectomy with contraletral cystectomy or bilateral cystectomy [19].

Aim of surgery in BOT should be complete macroscopic tumour resection, with adequate surgical staging including peritoneal biopsies, cytology and omentectomy (with appendicectomy for mucinous tumours if appendix is grossly abnormal). A great care should be taken so that the ovarian cyst, or mass, is removed intact, without spillage in both laparoscopy and laparotomy. Frozen section is not advisable as it can accurately predict only in 65% of cases, in 21% it can be upstaged to invasive cancer while in 25% it can even turn out to be benign [20]. Occasionally, a two staged approach is a favored as second surgery can be planned according to the histological findings.

In a comparison between BOT without micro-invasion (group1) and microinvasive BOT (group 2), the prognostic factors had no significant differences. Relapses after cystectomy, unilateral salpingo-oophorectomy and bilateral salpingo-oophorectomy were analysed between the 2 groups. In group 1 there were: 30%, 27.3%, and 0% and in group2: 29.4%, 12.1%, and 6.7%, respectively [21].

For stage I mucinous borderline tumours, the relapse rate is up to 10%. The risk of recurrence is least with bilateral salpingooophorectomy and maximum with ovarian cystectomy (30–40%). However, majority of recurrences are borderline which are easily salvageable [22].

Pregnancy rate is 54% in early stage disease and 34% in advanced stages after conservative management [23]. Natural fertility was maintained after fertility sparing surgery; only 9% required ART treatment [24].

Counselled: Completion surgery/ surveillance Patient was keen on surveillance **Follow up (6 months):** MRI: Complex right ovarian cyst 3.2 cm, left side ovarian endometrioma

Q: Further Management?

In the light of a new ovarian cyst, even a small recurrence shall be taken into consideration. The complex ovarian cyst needs further evaluation and description by USS. The patient would need repeated blood tests with full set of tumor markers (CA125, CEA, CA19.9, LDH, Alpha FP, Beta HCG). The patient also needs to be seen in the clinic and counselled depending on USS findings and blood results. If there are any concerning features on the USS, unilateral salpingo-oophorectomy shall be considered. The left ovarian endometrioma shall also be removed at the time of the surgery if the patient agrees for the procedure. If the patient chooses surveillance, she shall have a repeated USS and tumoral markers at 6 months, and if any worsening changes, surgery shall be recommended.

Case 4: Fertility Preservation in Ovarian Cancer

Age, Parity, PS	21-year-old, single ECOG = 0, BMI: 26
Clinical presentation	Referred with a histopathology diagnosis of clear cell ca of the left ovary on a background of endometriosis stage 1C1 (Fig. 29.3) Surgery done: Staging laparotomy with Left salpingo oophorectomy and infracolic omentectomy
Co morbidities	Nil

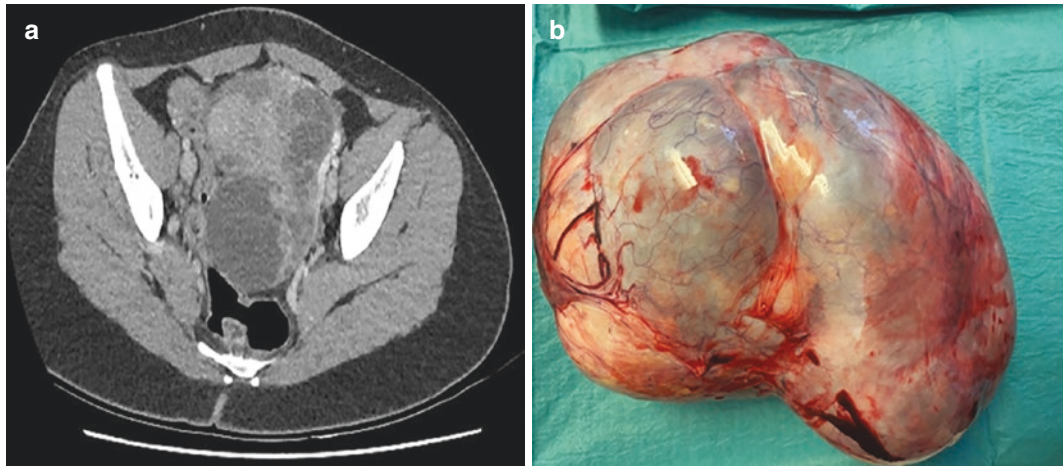


Fig. 29.3 (**a**) Contrast enhanced CT scan image showing a complex pelvic mass arising from? Left ovary. (**b**) Intraoperative specimen of 10 × 12 cm left ovarian mass

Q: How Should the Patient Be Counselled as She Is Very Keen on Fertility Preservation?

The patient should understand the fact that clear cell carcinoma is an aggressive type of ovarian cancer which does not respond to chemotherapy as opposed to other types of ovarian cancer (i.e. high grade serous). Early-stage clear cell ovarian cancer has a very good prognosis; however, completion surgery is the mainstay of the treatment. This case shall be discussed in the MDT for fertility sparing and the management discussed with the patient, with a careful assessment of the benefits and risks. Both surgical management as well as surveillance and completion of the treatment once family is completed should be discussed with the patient [62].

Q: What Are the Criteria for Fertility Preservation in Ovarian Cancer?

Fertility-sparing treatment in early-stage epithelial ovarian cancer can be considered following thorough discussion with the patient about the potential risk of recurrent epithelial ovarian cancer. The following are suitable for fertility preservation [25].

Disease related factors

- Stage 1A grade 1–2
- Stage 1C1, grade 1 or 2

Patient related factors

- Age of patient <40 years
- No contraindication to fertility
- Ovarian reserve assessment is normal

Fertility sparing is contraindicated in grade 3, 1C2, C3 tumours and clear cell cancer. These patients should be carefully informed about their prognosis, to enable them to make a personalised and informed choice.

Q: Discuss Oncologic Outcomes and Pregnancy Rates of Fertility Sparing Surgery in Ovarian Cancer

In a systematic review, the recurrence rates were 7% in stage IA grade 1 and 11% in stages IA grade 2 and IC grade 1/2 disease. The recurrence rate was higher in a subset of grade three tumours (29%) with 95% of the extra-ovarian recurrences and only 22% of them were rendered disease-free. Recurrence rates in 1C2/3 were 23% [26]. According to tumor histology the recurrence was

significantly high with clear cell histology (22%) and around 10–15 percent with others (mucinous, serous and endometrioid tumors).

The 10 year survival in the fertility sparing group is 89% which is similar to that of the conventional surgery group. In the high risk group (clear cell histology, grade 3, or stage IC), 10-year survival was 80.5% among women who underwent fertility-sparing surgery and 83.4% among those who had conventional surgery (hazard ratio 0.86) [27].

The successful pregnancy rate is reported as 30–37%, the rates being higher in women actively trying to conceive (66–100%) [28, 29]. Majority have spontaneous conception.

Spontaneous abortion rates are between 9–11% and live birth rate is 78%.

MDT decision: Completion surgery
Patient underwent
TAH + RSO + omentectomy+resection of enlarged lymph nodes
MDT plan: Adjuvant chemotherapy

Q: Effect of Chemotherapy on Future Fertility?

Chemotherapy may cause temporary or permanent infertility. The type and dose of chemotherapy have a major impact on the risk of gonadotoxicity.

There are different mechanisms associated with the ovarian toxicity of chemotherapy

- direct effect on double-strand DNA of the germ cells
- acceleration in follicular activation,
- indirect impact on the stroma leading to a decrease of blood vessels and reduction of blood supply.

In the case of temporary infertility, periods may become lighter or stop during treatment, however they will go back to normal in 6–12 months after completion of treatment. The woman can still get pregnant, and contraception is recommended, as chemotherapy can be detrimental to the fetus.

Q: Chemoprevention Strategies to Prevent Gonadotoxic Effect of Chemotherapy—How to Protect Ovarian Function Before and During Chemotherapy?

To prevent chemotherapy-induced premature ovarian insufficiency and early menopause-related symptoms, GnRH analogues can be administered during chemotherapy [30, 31]. Chemotherapy-induced gonadotoxicity involves all follicular stages and cell types, impairing both ovarian reserve and hormonal function through direct and indirect damages. Although the protective gonadal effect of GnRHa is not fully clear, it has indirect and direct effects on the ovaries.

Indirect effect. The administration of GnRHa induces an initial release of gonadotropin, which causes a desensitization of GnRH-receptors and prevents from the effects of pulsatile GnRH secretion (the "flare-up effect") [32]. This condition would be able to generate a hypogonadotropic state that keeps the follicles in a quiescent state, making them less vulnerable to chemo-induced damage. Proliferating follicles also release anti-müllerian hormone (AMH), which can negatively regulate the primordial follicles recruiting. During chemotherapy, AMH levels are usually dramatically lowered, causing a recruitment of primordial follicles, and exposing them to chemo-induced damage. It has been observed that the addition of GnRHa can raise AMH levels and prevent this effect [33].

Direct effect. GnRH receptors are expressed on the surface of the ovarian cells and their activation may result in an anti-apoptotic effect [34].

Key Points

1. For fertility preservation in gynecologic cancer, a personalised strategy with a multi disciplinary approach involving a gynecologic oncologist, medical and radiation oncologist and infertility specialist is crucial.
2. Fertility preservation in cervical cancer can be offered in squamous and adeno carcinomas upto stage 1B1. Surgical options include

conizaion, simple or radical trachelectomy depending on tumor size, stage, LVSI and margin status.

3. Endometrial cancer the candidates for fertility preservation include atypical hyperplasia and grade 1 endometrioid cancer stage 1A with no myometrial invasion. Options include oral progestogens as stand alone treatment or in combination with LNG IUS, GnRH analouges, hysteroscopic resection.
4. Fertlity sparing surgery can be done in BOT with favourable outcomes
5. In invasive ovarian cancer fertility preserving surgery may be done for grade 1–2 stage 1A and 1C1 cancer. Fertility sparing is contraindicated in grade 3, 1C2, C3 tumours and clear cell cancer

References

1. Murphy D, Klosky JL, Reed DR, et al. The importance of assessing priorities of reproductive health concerns among adolescent and young adult patients with cancer. Cancer. 2015;121:2529–36. https://doi.org/10.1002/cncr.29466.
2. Schmeler KM, et al. ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer. 2021;31:1317–25.
3. van Meurs H, Visser O, Buist MR, Ten Kate FJ, van der Velden J. Frequency of pelvic lymph node metastases and parametrial involvement in stage IA2 cervical cancer: a population-based study and literature review. Int J Gynecol Cancer. 2009;19(1):21–6. https://doi.org/10.1111/IGC.0b013e318197f3ef.
4. Burbano J, Heredia F, Sanabria D, Ardila EG, Viveros-Carreño D, Rodriguez J. Neoadjuvant chemotherapy prior to fertility-sparing surgery in cervical tumors larger than 2 cm: a systematic review on fertility and oncologic outcomes. Int J Gynecol Cancer. 2021;31(3):387–98. https://doi.org/10.1136/ijgc-2020-001765.
5. Bogani G, Chiappa V, Vinti D, Somigliana E, Filippi F, Murru G, Murgia F, Martinelli F, Ditto A, Raspagliesi F. Long-term results of fertility-sparing treatment for early-stage cervical cancer. Gynecol Oncol. 2019;154(1):89–94.
6. Moawad NS, Santamaria E, Rhoton-Vlasak A, Lightsey JL. Laparoscopic ovarian transposition before pelvic cancer treatment: ovarian function and fertility preservation. J Minim Invasive Gynecol. 2017;24(1):28–35.
7. Ghadjar P, Budach V, Köhler C, Jantke A, Marnitz S. Modern radiation therapy and potential fertility preservation strategies in patients with cervical cancer undergoing chemoradiation. Radiat Oncol. 2015;10:50.
8. Nezhat C, Roman RA, Rambhatla A, Nezhat F. Reproductive and oncologic outcomes after fertility-sparing surgery for early stage cervical cancer: a systematic review. Fertil Steril. 2020 Apr;113(4):685–703. https://doi.org/10.1016/j.fertnstert.2020.02.003.
9. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril. 2016;106(5):1195–1211.e5. https://doi.org/10.1016/j.fertnstert.2016.06.032; Epub 2016 Jul 16.
10. Fokom Domgue J, Schmeler KM. Conservative management of cervical cancer: current status and obstetrical implications. Best Pract Res Clin Obstet Gynaecol. 2019;55:79–92. https://doi.org/10.1016/j.bpobgyn.2018.06.009; Epub 2018 Jun 28.
11. Rodolakis A, Thomakos N. Fertility preservation for gynaecologic cancer patients. ESGO textbook of gynaecological oncology. 2017; 135:1065–1076.
12. Scholten AN, van Putten WL, Beerman H, Smit VT, Koper PC, Lybeert ML, et al. PORTEC Study Group. Postoperative radiotherapy for stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005;63(3):834–8.
13. Rodolakis A, Biliatis I, Morice P, et al. European Society of gynecological oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. Int J Gynecol Cancer. 2015;25:1258–65.
14. Qin Y, Yu Z, Yang J, Cao D, Yu M, Wang Y, Shen K. Oral progestin treatment for early-stage endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer. 2016;26(6):1081–91.
15. Daly MB, Pilarski R, Yurgelun MB, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 1.2020. J Natl Compr Cancer Netw. 2020;18:380–91.
16. Corrado G, Marchetti C, Trozzi R, Scambia G, Fagotti A. Fertility preservation in patients with BRCA mutations or lynch syndrome. Int J Gynecol Cancer. 2021;31(3):332–8. https://doi.org/10.1136/ijgc-2020-002071.
17. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266.e1–12.
18. Herrera Cappelletti E, Humann J, Torrejón R, Gambadauro P. Chances of pregnancy and live birth among women undergoing conservative management of early-stage endometrial cancer: a system-

atic review and meta-analysis. Hum Reprod Update. 2022;28(2):282–95.
19. Kim SS. Fertility preservation for women with borderline ovarian tumors: fertility-sparing surgery. Fertil Steril. 2021;115(1):83–4. https://doi.org/10.1016/j.fertnstert.2020.09.129; Epub 2020 Oct 12.
20. Ratnavelu ND, Brown AP, Mallett S, Scholten RJ, Patel A, Founta C, Galaal K, Cross P, Naik R. Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses. Cochrane Database Syst Rev. 2016;3(3):CD010360.
21. Ferrero A, Strada I, Marcoberardino BD, Maccarini LR, Pozzati F, Rossi M, et al. Clinical significance of microinvasion in borderline ovarian tumors and its impact on surgical management. Int J Gynecol Cancer. 2012;22(7):1158–62.
22. Gershenson DM. Management of borderline ovarian tumours. Best Pract Res Clin Obstet Gynaecol. 2017;41:49–59.
23. Daraï E, Fauvet R, Uzan C, Gouy S, Duvillard P, Morice P. Fertility and borderline ovarian tumor: a systematic review of conservative management, risk of recurrence and alternative options. Hum Reprod Update. 2013;19(2):151–66.
24. Johansen G, Dahm-Kähler P, Staf C, Flöter Rådestad A, Rodriguez-Wallberg KA. Reproductive and obstetrical outcomes with the overall survival of fertile-age women treated with fertility-sparing surgery for borderline ovarian tumors in Sweden: a prospective nationwide population-based study. Fertil Steril. 2021;115(1):157–63.
25. Floyd JL, Campbell S, Rauh-Hain JA, Woodard T. Fertility preservation in women with early-stage gynecologic cancer: optimizing oncologic and reproductive outcomes. Int J Gynecol Cancer. 2021;31(3):345–51. https://doi.org/10.1136/ijgc-2020-001328; Epub 2020 Jun 21.
26. Bentivegna E, Gouy S, Maulard A, Pautier P, Leary A, Colombo N, Morice P. Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues. Ann Oncol. 2016;27(11):1994–2004.
27. Melamed A, Rizzo AE, Nitecki R, Gockley AA, Bregar AJ, Schorge JO, Del Carmen MG, Rauh-Hain JA. All-cause mortality after fertility-sparing surgery for stage I epithelial ovarian cancer. Obstet Gynecol. 2017;130(1):71–9.
28. Fotopoulou C, Braicu I, Sehouli J. Fertility-sparing surgery in early epithelial ovarian cancer: a viable option? Obstet Gynecol Int. 2012;2012:238061. https://doi.org/10.1155/2012/238061; Epub 2012 Feb 23.
29. Gerstl B, Sullivan E, Vallejo M, et al. Reproductive outcomes following treatment for a gynecological cancer diagnosis: a systematic review. J Cancer Surviv. 2019;13:269–81.
30. Kitajima Y, Endo T, Nagasawa K, Manase K, Honnma H, Baba T, Hayashi T, Chiba H, Sawada N, Saito T. Hyperstimulation and a gonadotropin-releasing hormone agonist modulate ovarian vascular permeability by altering expression of the tight junction protein Claudin-5. Endocrinology. 2006;147:694–9.
31. The ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, Demeestere I, Dwek S, Frith L, Lambertini M, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020;2020:hoaa052.
32. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. Oncologist. 2007;12:1044–54.
33. Hasky N, Uri-Belapolsky S, Goldberg K, Miller I, Grossman H, Stemmer SM, Ben-Aharon I, Shalgi R. Gonadotrophin- releasing hormone agonists for fertility preservation: unraveling the enigma? Hum Reprod. 2015;30:1089–101.
34. Harrison GS, Wierman ME, Nett TM, Glode LM. Gonadotropin-releasing hormone and its receptor in normal and malignant cells. Endocr Relat Cancer. 2004;11:725–48.

Techniques of Assisted Conception in Gynaecological Oncology

30

James Cheshire, Trusha Kothari, and Lynne Robinson

Introduction

Undergoing treatment for gynaecological cancer during a woman's reproductive years, encompasses the added fears and worries about a woman's future fertility potential.

The field of fertility preservation has grown over the last two decades following the increased recognition of the detrimental effects that oncologic treatments can have on fertility potential. Despite this, there is limited data on fertility outcomes in these patients and women may face barriers in access to fertility preservation services.

Advancements in vitrification have meant that outcomes for women have improved and fertility preservation of embryos or oocytes can give women undergoing cancer treatment a security for the future. Gaps in healthcare professionals' knowledge exist around the options available or suitable for individual women, eligibility for funding, required window to undertake fertility preservation and available patient education material.

Women of childbearing age must be adequately counselled on;

1. The impact that their cancer and the recommended treatment will have on their reproductive function and future fertility potential
2. Their fertility preservation options
3. Issues relating to cryopreservation storage after fertility preservation
4. Funding restrictions - these will vary regionally however exclusion criteria will usually include age > 39, BMI >35 and existing children.
5. Fertility options available to them with their stored gametes or embryos and pregnancy following gonadotoxic treatment
6. Other options for parenthood such as adoption, use of donated gametes or surrogacy

Patients desiring fertility preservation should be individually assessed by a fertility specialist and the patient specific risks fully considered prior to undertaking any fertility preservation. Testing of anti-mullerian hormone and performing an antral follicle count can assess how successful a woman is likely to be in fertility treatment.

Options of fertility preservation available to women include: oocyte cryopreservation, embryo

J. Cheshire · T. Kothari
Birmingham Women's and Children's NHS Foundation Trust, Assisted Conception Unit, Birmingham, UK
e-mail: james.cheshire@nhs.net; trushak@doctors.org.uk

L. Robinson (✉)
Birmingham Womens & Children's NHS Foundation Trust, Gynaecology, Birmingham, UK
e-mail: lynne.robinson6@nhs.net

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_30

cryopreservation, ovarian tissue preservation, ovarian transposition and GnRH agonist protection. The use of the aromatase inhibitor letrozole for oestrogen sensitive tumours has also allowed this group of women to safely go through treatment.

These women require thorough counselling prior to any fertility preservation treatment on the limitations to treatment, the likelihood of success with stored gametes and embryos and the effect their treatment will have on their ovarian reserve and ability to carry a pregnancy in the future.

Following discharge from oncology services, women should have an early referral to fertility services if they wish to have a family. They should be assessed on their ability to conceive naturally and an assessment of ovarian reserve should be done. Any risks to pregnancy and recurrence of cancer should be identified and a multi-disciplinary approach between the oncologist, fertility specialist and obstetrician, with early referral to pre-pregnancy counselling if required.

Case 1

Age, Parity	32 years, nulliparous, BMI = 32
Presenting complaints	Irregular heavy periods and inter menstrual bleeding x 1 year Primary infertility × 2 years Partner has severe oligoasthenozoospermia Previous ultrasound scan showed endometrial thickness of 14 m, presence of polycystic ovarian morphology
Comorbidities	Nil
Transvaginal sonography	Uterus normal size, endometrial thickness = 21 mm, bilateral adnexa show polycystic ovaries
Endometrial biopsy	Grade 1 endometrioid cancer
MRI	Endometrium thickened 20 mm, no myometrial invasion seen Pelvic lymph nodes not enlarged, bilateral ovaries normal
Treatment	Levonorgestrel intrauterine system + oral megestrol acetate × 10 months Showed complete regression of endometrial cancer at 12 months

Discuss the Work Up for Assessment of Fertility Potential of this Couple

This patient should be seen in a fertility outpatient clinic. A thorough history should be taken, focusing on their gynaecological past medical or surgical history. The patient's overall suitability to undergo fertility treatment and a planned pregnancy should be assessed. Any issues identified may require a referral for pre-pregnancy counselling.

In view of the partners seminal fluid analysis showing severe oligoasthenozoospermia the recommended treatment of choice would be intracytoplasmic sperm injection (ICSI), to optimise the likelihood of successful fertilisation. Depending on the severity of the oligoasthenozoospermia, sperm banking could be considered if there are concerns around impending testicular failure (indicated by raised FSH/LH and low Testosterone). If sperm concentration is <5mil/ml and/or poor motility (<32%) then a full male diagnostic work up should be performed.

The female patient will need an AMH blood test to measure her ovarian reserve. This will determine whether fertility treatment is possible in the first instance and guide management with regards to suitable treatment protocol and dose. A pelvic ultrasound should be performed on the fertility unit to assess her endometrial lining, uterine cavity (for presence of fibroids/polyps) and to assess the ovaries for an antral follicle count and to ensure that they will be accessible via a transvaginal approach during future egg collection. Currently due to patients BMI > 30 the couple would have to self-fund their fertility treatment until they optimised their BMI. Patient's with a BMI >35 would not be considered suitable for any fertility treatment.

A multi-disciplinary approach is essential when dealing with this patient, close communication regarding timing of treatment and removal of the IUS to limit impact of treatment is important.

What Are the Treatment Options?

This couple would be suitable for ICSI treatment due to the male factor cause (severe oligoasthenozoospermia). As the patient has polycystic ovarian morphology a short GnRH antagonist protocol should be used with a GnRH agonist trigger and a plan to freeze any embryos formed to minimise the risks of ovarian hyperstimulation syndrome. This also means the IUS can remain in situ during stimulation.

What Are the Success Rates of Fertility Treatment?

There is little evidence looking at the use of stored gametes and embryos following fertility preservation for oncologic reasons. Age at oocyte cryopreservation and indication for oocyte cryopreservation both have an impact on the cumulative live birth rate, with an age over 36 leading to poorer outcomes. One study found the live birth rate in oncology patients undergoing fertility preservation was 41.1%, this is in comparison to 68.8% in women undergoing oocyte preservation for age-related fertility decline [1].

Adverse Impact of Assisted Conception in this Case

There is an increased risk of ovarian hyperstimulation syndrome (OHSS) during/following controlled ovarian stimulation with gonadotropins, especially in women with polycystic ovaries. To minimise this risk a GnRH antagonist protocol should be selected with a GnRH agonist trigger to cause final oocyte maturation. This approach significantly reduces the risk of OHSS.

Two systematic reviews have looked at pregnancy outcomes after endometrial cancer. Gunderson et al. [2] reviewed outcomes in 315 women who received hormonal treatment for grade 1 adenocarcinoma or endometrial hypertrophy. Reproductive outcomes (i.e. live births) did not differ between the cohorts with different endocrine treatments. A review by Chao et al. [3] looking at obstetric outcomes in 50 patients with early stage endometrial cancer (grade 1 or 2) who conceived after progesterone treatment found that there was a significant increase in hypertensive disorders, preterm birth, multiple pregnancies and caesarean section in women who conceived after ART compared to women who conceived spontaneously or had ovulation induction with intrauterine insemination. Referral to pre pregnancy counselling is therefore strongly advised.

Oncological outcomes were reported by Gunderson et al. [2]. They reported a recurrence rate of 35.4% in the carcinoma cohort and 23.2% in the hyperplasia group, with a median time to recurrence of 24 months (range from 4 to 72 months). The review however did not investigate a possible association between recurrence and pregnancy. Women with a history of endometrial cancer should therefore be carefully monitored following fertility treatment by an oncologist due to the risk of relapse and strongly advised to proceed to hysterectomy once their family is complete.

One systematic review found that following progesterone treatment and regression of disease, out of 286 pregnancies, 69.4% led to a live birth, 66.7% were achieved through fertility treatment [4]. The literature suggests that the live birth rate following early-stage endometrial cancer is between 20.5% and 26.7% [4, 5].

This case should be handled in a multidisciplinary approach with close communication between the oncology and fertility team. This patient is at risk of excessive oestrogen exposure if she requires a couple of frozen embryo transfers and would need discussion regarding whether to perform another endometrial biopsy between repeated cycles.

Case 2

Age, Parity	21 years, single, BMI = 32
History	Staging laparotomy with left salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy HPE: Stage I C1 mucinous ovarian cancer (expansile and infiltrative pattern), ER, PR negative (previous history of left ovarian cystectomy done for mucinous borderline ovarian tumour (intestinal type) 1 year back) Received 6 cycles carboplatin +paclitaxel
Comorbidities	Nil
Treatment	Concerns about recurrence in opposite. Needs oocyte preservation, not in a relationship

Effect of Chemotherapy on Future Fertility?

Evidence in breast cancer patients show that the age of the patient at the time of exposure to cyclophosphamide based regimens determines the degree of risk of treatment induced gonadotoxicity and resultant amenorrhea.

Extrapolating from breast cancer data [6], given her age of 21 years, her risk of amenorrhea is <20% (compared to 40–60% risk of amenorrhoea in 30–39 years old and > 80% in over 40 years old). Patients with a cyclophosphamide based chemotherapy regimens are at high risk of treatment induced gonadotoxicity (>80% risk of amenorrhoea).

It should be noted however that return of periods following chemotherapy is a poor prognostic indicator for ovarian reserve. Patients who have had prior chemotherapy or radiotherapy to their abdomen and pelvis should have their ovarian reserve assessed in the form of an AMH blood test to determine whether undertaking fertility treatment is even possible.

What Are the Options for Fertility Preservation in this Case?

If there is enough time prior to management of a possible recurrence, this patient has the option of oocyte cryopreservation from her remaining right ovary. Another option could be ovarian tissue cryopreservation.

Timely referral to a fertility unit will be necessary to assess this patients' suitability for cryopreservation of her oocytes. A careful history should be taken and the return of periods and regularity of any cycle may be helpful in counselling the patient about her ovarian reserve. The patient's AMH levels should be obtained to determine their ovarian reserve which is likely to have been impacted by the chemotherapy and subsequent removal on her left ovary. This will determine whether oocyte cryopreservation is likely to be successful given the likely reduced fertility potential. It is important to note that patient age and ovarian reserve dramatically affects the success of oocyte cryopreservation. One prospective study [7], in the non-cancer population, demonstrated that the proportion of frozen oocytes resulting in live birth was 8.2% in women under 36 years (12.1 oocytes required per live birth) compared to 3.3% in women 36–39 years (29.6 oocytes required per live birth). This is likely to be lower in the cancer population.

Prior to undertaking any fertility treatment a transvaginal pelvic ultrasound should be undertaken to ensure the remaining ovary appears normal and determine its accessibility for a transvaginal approach to oocyte collection and to perform an antral follicle count. If there are any concerns about the appearance of the remaining ovary an oncological opinion must be sought prior to any oocyte retrieval.

The patient should be adequately counselled by the fertility unit around the process of cryopreservation and future use of her frozen oocytes. The expected survival of frozen oocytes (81–89%) and the expected success rates of frozen oocytes in achieving a live birth must also be discussed.

Explain the Regulations around Oocyte Preservation, How Long Can They Be Preserved

Prior to undertaking oocyte cryopreservation the patient will have consented to how long they want their oocytes to be stored for, what should happen to their oocytes if they were to die or

become unable to make decisions for themselves, whether the oocytes are to be used for their own treatment only, or whether they can be donated for someone else's treatment, or used for research or training if no longer want to store them.

Recent legislation has been introduced to enable cryopreserved oocytes and embryos to be stored for up to 55 years (previously 10 years). The patients' desire for ongoing storage will be reviewed with the fertility centre at regular intervals and extended if desired.

Women must also be made aware of NHS funding restrictions. Each clinical commissioning group will have its own criteria but these usually include age, BMI and any existing children. In addition, any funding for oocyte cryopreservation does not automatically extend to oocyte usage and the patient will need to be assessed against criteria again at the time of oocyte usage.

Case 3

Age, Parity	28 years, single, BMI = 26
History	Right ovarian mass; AFP: 800, HCG 2.0, LDH 240 Staging laparotomy with right salpingo-oophorectomy, infracolic omentectomy HPE: Yolk sac tumor stage 1C1 Referred for chemotherapy: BEPx 4 cycles
Comorbidities	Nil

Benefits of Ovarian Suppression with Gonadotropins and Other Chemoprevention Strategies to Reduce the Impact of Chemotherapy on the Remaining Ovary

In premenopausal women undergoing chemotherapy, the resultant treatment-induced premature ovarian insufficiency can negatively impact on the quality and wellbeing of the patients' life. The use of a GnRH agonist as a strategy to provide some degree of ovarian protection has been studied.

The evidence for the use of a GnRH agonist in providing a degree of ovarian protection comes largely from breast cancer patients. In women who had undergone chemotherapy alongside a GnRH agonist, the rate of chemotherapy induced ovarian insufficiency was 14.1% compared to 30.9% in those that did not receive a GnRH agonist alongside their chemotherapy [8]. The ovarian protection effect was still present when confounding factors such as age, oestrogen receptor status, type and duration of chemotherapy were adjusted for. In the only study [9] that has looked at post-treatment pregnancies as pre-planned secondary endpoint, the 5-year cumulative pregnancy incidence was significantly higher in the chemotherapy plus GnRH agonist arm as compared to the chemotherapy alone arm (23.1% vs. 12.2%; OR 2.34; 95% CI 1.07–5.11). This was however a small sample size and larger studies would be useful to further verify this.

With regards to its safety profile no detrimental effect on survival outcomes has been observed with the concurrent use of a GnRH agonist [8, 10].

Evidence on the efficacy and safety of GnRH agonists as a strategy for ovarian protection in other malignancies is limited to lymphoma and ovarian malignancies. For lymphoma, no clear difference in rates of chemotherapy induced ovarian insufficiency was observed between patients receiving GnRH agonist treatment or not [11]. For ovarian cancer patients, the only small available trial showed a potential effect in terms of ovarian function protection but did not report on fertility outcomes [12].

Due the limited availability of evidence for non-breast related malignancies, ESHRE guidance [6] suggests that outside of breast cancer the use of GnRH agonists may be considered for ovarian protection when oocyte/embryo cryopreservation is not possible.

Discuss the Assessment of Fertility Potential

The patient will need their AMH levels measured to determine her residual ovarian reserve. This will determine whether undertaking fertility

treatment is possible in the first instance and will subsequently guide further management with regards to suitable treatment protocol and dose to maximise egg yield.

When Should She Consider Assisted Conception and What Are the Available Options

Early referral to a fertility unit is strongly recommended in any patients who have either undergone surgery for gynaecological malignancies or chemo/radiotherapy for any malignancy.

An interval of at least 1 year following chemotherapy completion and a stable disease state is suggested before attempting a pregnancy in order to reduce the risk of pregnancy complications.

Given the fact that the patient has only one remaining ovary and has undergone 4 cycles of BEP chemotherapy her ovarian reserve is likely to be reduced. Whilst ovarian reserve levels cannot predict a patients' ability to conceive naturally, low ovarian reserve can identify patients at risk of premature ovarian insufficiency and resultant subfertility.

Early referral can therefore identify those patients at risk of premature ovarian insufficiency and ensure early counselling regarding their future fertility options. A realistic approach should be taken regarding fertility potential even though outcomes from platinum-based chemotherapies are good and options such as donor oocytes discussed.

If her ovarian reserve is high enough to undertake ovarian stimulation she could consider donor sperm IVF. If her ovarian reserve was too low for own oocyte treatment then the use of donor oocytes and donor sperm will be required.

Fertility Outcomes in Germ Cell Tumour After Treatment?

There is limited evidence regarding outcomes post germ cell tumours but in general they are favourable. A retrospective multicentre study looking at reproductive outcomes in patients with malignant ovarian germ cell tumours found that 42 of the 45 patients that desired childbirth conceived and 40 had successful deliveries. Seven of these patients required fertility treatment however only two required assisted reproductive technology. The median time to pregnancy was 4.4 years. No significant obstetric complications were identified [13].

Case 4

Age, Parity	26 years, nulliparous, BMI = 26
History	Radical trachelectomy for stage 1b1 squamous cell cancer cervix with cervical cerclage 2 years previously Regular periods with dysmenorrhea USG: Fluid collection in uterine cavity, cervical length 1.5 cm Trying to conceive for 1.5 years
Comorbidities	Nil

Diagnostic Work Up for this Case

Carrying a pregnancy following a radical trachelectomy is possible if the corpus uteri is preserved; however, these women should be managed as high risk due to the associated obstetric complications. Women are at risk of: preterm delivery, premature prelabour rupture of membranes, miscarriage, uterovaginal anastomosis varices causing abnormal bleeding during pregnancy and possible placenta mediated disease due to ligation of uterine arteries. Early referral should be made to the pre-pregnancy counselling clinic.

This patient should be seen in a fertility outpatient clinic. During this appointment a thorough medical/surgical/gynaecology history should be conducted. The patient's overall suitability to undergo fertility treatment and a planned pregnancy should be assessed.

The female patient will need an AMH blood test to measure her ovarian reserve. This will determine whether fertility treatment using her own eggs is possible in the first instance and guide management with regards to suitable treatment protocol and dose.

A pelvic ultrasound should be performed to assess uterine cavity and size, endometrial lining and to ensure that the ovaries will be accessible via a transvaginal approach during future egg collection.

The presence of a fluid collection in the uterine cavity should raise suspicion of a stenosed residual cervical canal and possible haematometra. This will impede implantation of an embryo in addition to an embryo transfer being difficult so prior to undertaking any fertility treatment an assessment of the patency of the cervical canal (in the form of a mock embryo transfer) must be undertaken to ensure it is possible to enter the uterine cavity transvaginally. If it is not possible to enter the uterine cavity through the residual cervical canal, either dilatation with hysteroscopy prior to the procedure or a transmyometrial approach should be considered. If a trans-cervical approach is possible a repeat mock embryo transfer should be repeated post hysteroscopy to ensure easy access and to measure the length of the cavity as this will be shorter due to the trachelectomy.

A seminal fluid analysis should be arranged for the partner to assess sperm parameters and determine whether IVF or ICSI treatment is required.

Treatment Options

Given that this patient has a regular cycle and therefore is likely ovulating regularly, the most suitable option would be IVF or ICSI depending on the semen analysis. The patient will require pre-pregnancy counselling by a suitable obstetrician and must be aware that there may be an increased risk of preterm labour because of the absence of the cervix and that a caesarean section is required for delivery due to the cervical cerclage.

Case 5

Age, Parity	35 years nulliparous BMI 30
History	History of rectal cancer 2 years ago. Had received neoadjuvant chemo RT followed by low anterior resection with anastomosis and defunctioning ileostomy (reversed later) Lynch syndrome positive (MSH 2 variant identified) Mirena coil in situ for endometrial protection Uses transdermal estrogen only patch
Comorbidities	Nil

What Is the Fertility Treatment to Be Considered in the Present Case?

This patient has been exposed to the gonadotoxic effects of chemotherapy and radiotherapy, the patient's ovarian reserve (in the form of an AMH level) would need to be assessed to determine whether the use of the patient's own eggs for fertility treatment is possible. She likely has primary ovarian insufficiency as she is on hormonal replacement therapy.

If use of the patient's own eggs is deemed possible then given that the patient carries the MSH 2 variant for Lynch syndrome, the patient should be offered genetic counselling and be offered treatment at a unit that can provide pre-implantation genetic testing for monogenetic disease (PGT-M) if she wishes. She must have a good ovarian reserve to make PGT-M a realistic possibility so in this scenario it is unlikely to be an option.

If the patient's own ovarian reserve is deemed too low to undertake fertility treatment then the use of donor eggs should be considered and the consideration of a surrogate if there is uterine scarring due to the history of pelvic irradiation.

Pelvic radiotherapy has been shown to have a significantly detrimental effect on obstetric outcomes. The incidence of spontaneous miscarriage (37% vs 7%) and preterm birth (63% vs. 18%) were significantly higher in patients with a history of pelvic irradiation [14]. Additionally structural and

functional uterine changes resulting from irradiation may affect embryo implantation and the ability to maintain a pregnancy, significantly increasing the risk of placental attachment disorders (placenta accreta or percreta), low birth weight, fetal malposition and perinatal death [15]. The patient should be adequately counselled about these risks and the option of surrogacy should also be discussed. Any pregnancy in a patient with a history of pelvic irradiation must be treated as high risk and managed in a centre with tertiary maternity services. If surrogacy is recommended, patients are very likely to have to entirely self-fund this treatment.

What Is the Role of Assisted Conception in this Patient as She Is High Risk for Endometrial Cancer and Needs Endometrial Protection Long Term?

The likelihood that this patient will be suitable for assisted conception is small. Given the fact that she is using hormonal replacement therapy, her ovarian reserve is likely to be low. As well as this, the history of pelvic irradiation may mean she is unlikely to be able to carry a pregnancy. Her best chance of success would be with donor eggs and surrogacy. It is important in these circumstances to discuss other options of parenthood, including adoption.

Once the patient has concluded her family, her risk-reducing surgery, in the form of a total hysterectomy and bilateral salpingo-oophorectomy, can be planned to prevent future gynaecological cancer.

Intra-Abdominal Adhesions Secondary to Surgery Could Increase Risk of Subfertility and Chances of Ectopic. What Precautions Should Be Taken?

During any abdominal surgery in a woman of reproductive age, it is essential to consider their future fertility, only perform necessary operations and consider fertility sparing surgery if they have not yet completed their family. Discussion around the consequences on any surgery should be fully discussed and implications of surgery to future fertility potential should be fully known. The use of barrier agents such as oxidised regenerated cellulose, polytetrafluoroethylene and fibrin or collagen for adhesion prevention in gynaecological surgery could prevent extensive adhesions and prevent tubal scarring or improve access to ovarian tissue during fertility treatment. Ovarian transposition may be considered in women undergoing pelvic irradiation to remove the ovaries from the harmful effects of radiation to preserve ovarian function. One systematic review found that ovarian function preservation following ovarian transposition and pelvic radiotherapy with, or without chemotherapy was 61.7% [16]. However, ovarian transposition will move the ovaries out of the pelvis making spontaneous conception unlikely and if assisted conception is desired, a transabdominal oocyte retrieval would be necessary as the ovaries will not be accessible transvaginally. This may confer added risk and may lead to a lower oocyte yield.

Key Points

- Fertility issues are common in women undergoing treatment for gynaecological cancers in premenopausal women
- Close liaison with the fertility and oncological team is able to achieve the best desirable outcome
- Oncological safety should not be compromised by the desire for fertility preservation and fertility treatments
- Fertility preservation is reserved for early stage gynaecological cancers where the survival of these patients is good.
- Preimplantation genetic testing is helpful in familial cancers associated with genetic mutation.

References

1. Cobo A, García-Velasco J, Domingo J, Pellicer A, Remohí J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod. 2018;33(12):2222–31.

2. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol. 2012;125(2):477–82.
3. Chao A-S, Chao A, Wang C-J, Lai C-H, Wang H-S. Obstetric outcomes of pregnancy after conservative treatment of endometrial cancer: case series and literature review. Taiwan J Obstet Gynecol. 2011;50(1):62–6.
4. Herrera Cappelletti E, Humann J, Torrejón R, Gambadauro P. Chances of pregnancy and live birth among women undergoing conservative management of early-stage endometrial cancer: a systematic review and meta-analysis. Hum Reprod Update. 2021;28(2):282–95.
5. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2012;207(4):266.e1–266.e12.
6. The ESHRE Guideline Group on Female Fertility Preservation. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020;2020(4):hoaa052.
7. Bracewell-Milnes T, Norman-Taylor J, Nikolaou D. Social egg freezing should be offered to single women approaching their late thirties: AGAINST: women should be freezing their eggs earlier. BJOG. 2018;125(12):1580.
8. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36(19):1981–90.
9. Moore HCF, Unger JM, Phillips KA, Boyle F, Hitre E, Moseley A, et al. Final analysis of the prevention of early menopause study (POEMS)/SWOG intergroup S0230. J Natl Cancer Inst. 2019;111(2):210–3.
10. Regan MM, Walley BA, Francis PA, Fleming GF, Láng I, Gómez HL, et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. Ann Oncol. 2017;28(9):2225–32.
11. Senra JC, Roque M, Talim MCT, Reis FM, Tavares RLC. Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51(1):77–86.
12. Gilani MM, Hasanzadeh M, Ghaemmaghami F, Ramazanzadeh F. Ovarian preservation with gonadotropin-releasing hormone analog during chemotherapy. Asia Pac J Clin Oncol. 2007;3(2):79–83.
13. Tamauchi S, Kajiyama H, Yoshihara M, Ikeda Y, Yoshikawa N, Nishino K, et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study. Am J Obstet Gynecol. 2018;219(4):385.e1–7.
14. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood. 1996;87(7):3045–52.
15. Tarín JJ, García-Pérez MA, Cano A. Obstetric and offspring risks of women's morbid conditions linked to prior anticancer treatments. Reprod Biol Endocrinol. 2016;14(1):37.
16. Buonomo B, Multinu F, Casarin J, Betella I, Zanagnolo V, Aletti G, et al. Ovarian transposition in patients with cervical cancer prior to pelvic radiotherapy: a systematic review. Int J Gynecol Cancer. 2021;31(3):360–70.

Part VIII

Miscellaneous

31 Hereditary Gynaecologic Cancer Syndromes

Aarti Lakhiani

Introduction

Hereditary gynaecologic cancer syndromes (HGCS) are a collection of genetic causes of gynaecological cancers. Approximately 5–10% of all cancers can be attributed to hereditary cancer syndromes [1]. The most significant HGCS include BRCA1 and BRCA2 mutations, which predisposes to breast and ovarian cancer. Lynch syndrome, another notable syndrome, increases the risk of endometrial and ovarian cancers, and predisposes women to other, non-gynaecologic cancers such as colorectal, small intestine, and stomach cancer.

A woman's genetic makeup and family history determine her inherent risk for getting certain gynaecological cancer. If a close or immediate family member has had breast or ovarian cancer, this increases the likelihood of having a HGCS. Hereditary gynaecological cancers typically present at much younger ages than sporadic cancers. Investigating for the presence of a hereditary cancer syndrome allows healthcare professionals to offer an individualised and quantified assessment of a person's cancer risk, as well as options for tailored screening and prevention strategies that may reduce morbidity associated with the development of malignancy.

A. Lakhiani (✉)
Pan Birmingham Gynaecological Cancer Centre, City Hospital, Birmingham, UK
e-mail: aartilakhiani@nhs.net

In this chapter we will review cases of hereditary cancers, their management and prognosis.

Case 1: Lynch Syndrome

Age, Parity, PS	45 years old, P3 + 0, PS-0
Clinical presentation	TAH + BSO+ pelvic and paraaortic lymphadenectomy
Histology	Endometrioid ca endometrium stage 1A, grade 1(size: 4.5 cm), moderately differentiated with <50%myoinvasion, LVSI negative, tubes and ovaries not involved, lymph nodes 0/9
Family history	Sister- uterine cancer at age 40, died within 1 year of diagnosis Paternal aunt (55 years old)- history of colon cancer

Gynaecological cancers, especially endometrial cancer (EC), are often the sentinel cancer in the patients with Lynch syndrome (LS) [2]. Two to five percent of EC can be attributed to LS [3]. LS is an autosomal dominantly inherited cancer syndrome which predisposes to colorectal, endometrial, ovarian and other cancers [4]. It is caused by a mutation in one of the mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2 [5–7]. Around 70–90% of Lynch syndrome is attributable to deleterious mutations in MLH1 and MSH2, with the remaining 10–30% distributed approximately equally between MSH6 and PMS2 [8].

K. Singh, B. Gupta (eds.), *Case-Based Gynecological Oncology*,
https://doi.org/10.1007/978-3-031-36179-1_31

Identifying Lynch syndrome at the point of EC cancer diagnosis could:

1. prevent other cancers in people with LS (such as colorectal cancer) through increased surveillance and strategies to reduce risk,
2. help to identify relatives with LS, to reduce their risk of Lynch syndrome-associated cancers or increase early detection of cancer,
3. help relatives diagnosed at an early age to consider family planning and, if they wish, have risk-reducing interventions, for example, a hysterectomy [9].

In 2020, National Institute of Health and Care Excellence (NICE) published a stepwise testing strategy (diagnostics guidance DG42) for LS in people with endometrial cancer including MMR protein immunohistochemistry, MLH1 promoter methylation and germline testing (Fig. 31.1). All patients with EC should be offered testing for LS. Testing is done on tumour tissue by immunohistochemistry for MMR proteins, then MLH1 promoter hypermethylation if needed. If the results show that Lynch syndrome is likely, further tests are offered to confirm this.

Historically the Amsterdam criteria-2 (AC-2) was used to identify LS [10]. This follows a 3:2:1 rule and includes:

1. ≥3 relatives related by a first degree relationship with a LS cancer*,
2. these LS cancers should span ≥2 generations,
3. one (or more) of these cancers is <50 years.

However, given the poor sensitivity of AC-2, the Bethesda criteria were introduced and used at cancer diagnosis to determine which tumour samples should undergo molecular analysis via

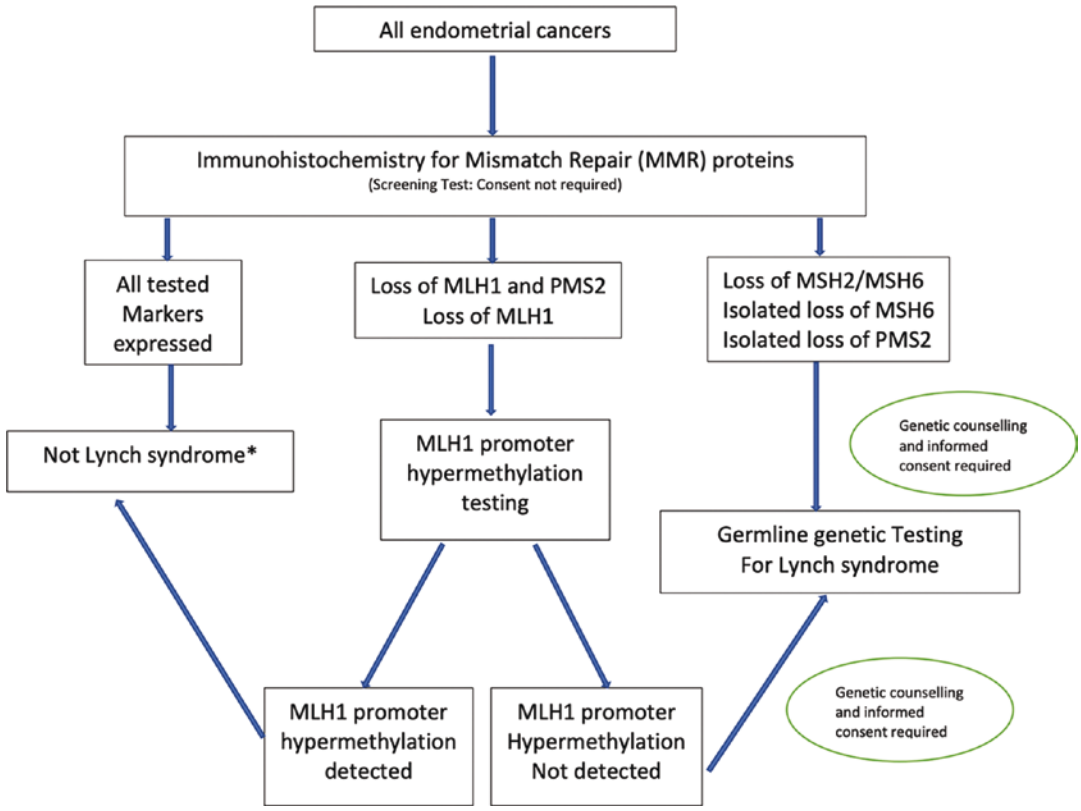


Fig. 31.1 NICE in DG42- Flow chart of the proposed pathway

microsatellite instability (MSI) or immunohistochemistry (IHC) to identify MMR deficiency and enable subsequent triage for MMR gene testing [10]:

- Developing colorectal cancer (CRC) or EC younger than age 50
- Developing CRC, EC, or other type of cancer* with mismatch repair deficiency (MMR-D) or high-level microsatellite instability (MSI-H) found after testing of a sample of the tumour
- Developing CRC and other types of cancer* linked with Lynch syndrome separately or at the same time
- CRC in 1 or more first-degree relatives who also has or has had another Lynch syndrome-related cancer*, with 1 of these cancers developing before age 50. The phrase "first-degree relatives" includes parents, siblings, and children.
- CRC in 2 or more first- or second-degree relatives with another Lynch syndrome-related cancer*. "Second-degree relatives" include aunts, uncles, grandparents, grandchildren, nephews, and nieces.

*Category includes CRC, EC, ovarian cancer, stomach cancer, small bowel cancer, ureter or renal pelvis cancer, bladder cancer, bile duct cancer, pancreatic cancer, or sebaceous adenomas of the skin

Implications of MMR Testing on Patient Management

MMR status has several clinical implications in the management of cancer patients. In addition to identifying patients with EC caused by LS, tumour molecular features, including MMR-deficiency, may improve prognostication and help guide adjuvant therapy for EC patients [11]. MMR deficiency is also associated with improved overall survival in women with nonmetastatic endometrial cancer [12].

Implications of Lynch Testing on Other Disease Screening

There can be considerable anxiety and uncertainty associated with genetic testing for hereditary cancer syndromes such as LS. These test results can have a substantial effect on a person, so it is very important that people understand the full implications of a diagnosis of LS, for themselves and their families.

The identification of Lynch syndrome after a diagnosis of EC means interventions and surveillance can be implemented to reduce the risk of other LS-associated cancers or detect them earlier. CRC screening and prevention involves 1-2yearly colonoscopy and daily aspirin intake [13, 14]. There is a well-documented survival advantage for those with LS who are compliant with surveillance for CRC [7].

For LS-associated cancers other than CRC and EC, the symptoms of these cancers can be highlighted to make sure people seek medical advice if they have symptoms. There is no proven benefit to the available screening tests for these cancers.

Implication on Other Family Members

A diagnosis of LS firstly allows testing for the condition to be offered to relatives, who can be identified as having LS before they have cancer. If a person knows they have LS, they can make lifestyle changes, e.g. stop smoking, to help reduce their cancer risk.

Knowing that they are at higher risk of gynaecological cancer may help people make decisions about family planning. Options for LS carriers include prophylactic hysterectomy and bilateral salpingo-oophorectomy as the most effective intervention to prevent EC and OC. This is usually offered after the age of 40 years once their family is complete. Routine transvaginal ultrasound (TVS) and CA-125 screening for ovarian cancer

(OC) is not typically recommended because these screening tests have not been shown to be sufficiently sensitive or specific [14, 15].

Although the evidence base for EC screening in high-risk women is limited, case series show it can detect both complex atypical hyperplasia and early cancer, although interval cancers may still occur [16–19]. EC screening may have a role to play in women with LS who wish to delay surgical prevention, and is usually undertaken every 1–2 years from 35 years. EC-screening options involve annual TVS and endometrial sampling alone or outpatient hysteroscopy plus endometrial sampling. TVS alone without endometrial sampling is not effective. Because EC often presents at an early stage with symptoms of abnormal uterine bleeding, all women with LS should be advised to report these symptoms promptly [20].

Impact on Insurance

If you have not had cancer and have been offered a genetic test because there is a known mutation in the family or because no family members with cancer can be offered a genetic test, you are having a predictive genetic test. There is an agreed Code of Practice amongst members of the Association for British Insurers (ABI) that information about predictive genetic tests for cancer predisposition gene mutations is not used by insurance companies to determine if a policy is offered, or to determine the cost of the policy. Insurance companies who are signed up to the Code will never require or pressure any applicant to undertake a predictive or diagnostic genetic test and will only consider the result of a predictive genetic test for a very small minority of cases. They will also not ask for or take into account the results of a predictive genetic test if you are applying for insurance. The only exception being if you are applying for life insurance over £500,000 or if the patient has had a predictive genetic test for Huntington's disease. Only in this circumstance do you need to tell the insurance company the result of the test, if they ask.

These insurance companies recognised that a diagnostic genetic test is the same as any other diagnostic medical test (such as a blood test). This means you might need to tell the insurance company about the results of a diagnostic genetic test when you apply for insurance. You may be asked for this information as part of the application form, or it may be included in your medical report if the insurance company asks to see it as part of your application, and the GP thinks the test is relevant.

Case 2: BRCA Positive Ovarian and Breast Cancer

Age, Parity, PS	41 years old, P2 + 0, PS-2
Clinical presentation	Presented with vomiting and abdominal distensionx 2 months
Past medical history	Right breast cancer 2 years ago, managed with a wide local excision. Histopathological: Invasive ductal carcinoma, grade 3, ER-ve, PR-ve, HER2/neu negative Required DJ stenting for right hydronephrosis 1 year ago, received ATT ×6 months
Examination	Ascites+, large fixed mass arising from pelvis, nodules in pouch of Douglas
Investigations	*PET CT*: Ascites+ FDG avid mass 11 × 7.7 × 8 cm arising from pelvis most likely from left adnexa. Multiple nodules (FDG avid) in the peritoneum, largest 3 × 4 cm near umbilicus Nodules in posterior pelvic peritoneum, anterior surface of bladder, loss of fat planes between mass and sigmoid colon Right side hydronephrosis *Biopsy from adnexal mass*: Adenocarcinoma, WT1 + ve, PAX8 positive, CK7 positive, ER+, PR negative *Tumour markers*: CA125: 692, CEA: 9, CA15.3: 9.2
Management	Neoadjuvant chemotherapy × 4 cycles Interval debulking surgery: TAH + BSO+ anterior peritonectomy +Supracolic omentectomy (R0 resection) Germline BRCA 1 positive

Screening in Ovarian Cancer

There are two main types of screening- predictive and mainstream screening.

Predictive screening involves the use of a genetic test to determine if an asymptomatic individual has a gene variant which may cause disease in the future. It can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. This can then provide information about a person's risk of developing a specific disorder and help with making decisions about medical care. Unlike mainstream screening, predictive screening involves clinical geneticists.

In mainstream screening, non-genetic healthcare professionals identify at-risk individuals and initiating genetics discussions by integrating genetics into clinical practice. They provide pre-test counselling (e.g. review cancer family history, discuss possible implications of a genetic test) and order the genetic test after obtaining informed consent. These professionals are not formally trained as genetic counsellors or clinical geneticists. It enables genetic testing to be more accessible to all patients who might benefit from it. Mainstream screening is now part of standard NHS clinical practice [21, 22].

Germline and Somatic Tests

Around 11–18% of OC have germline BRCA1/BRCA2 mutations and another 6–9% have a somatic BRCA1/BRCA2 mutations in the tumour tissue alone which is not inherited [21]. Thus two-thirds of BRCA mutations in tumour tissue originate from the germline, but one-third are somatic.

Germline mutations occur in sperm, eggs, and their progenitor cells and are therefore heritable. Germline testing is a type of DNA testing that looks for germline mutations, or inherited predispositions to certain types of cancers. It can be done via cheek swab, spit sample or more commonly, a blood sample. BRCA1/BRCA2 mutations are well-known examples of germline mutations that increases someone's risk for ovarian and breast cancer. It is important to note that germline testing cannot detect cancer. It can only determine if someone has a predisposition for a particular kind of cancer based on genes inherited from a parent.

Somatic or tumour testing is another form of genetic testing, but unlike germline testing, which looks for inherited mutations, somatic testing is looking for acquired mutations in a confined set of cells or tissue. While germline mutations are in every cell in the body and have been there since birth, somatic mutations are typically isolated to the tumour or area where cancer exists in the body. Somatic mutations cannot be inherited by offspring. It is possible for a BRCA mutation to be an acquired mutation and not an inherited one. This is why it is important to have both germline and somatic testing when one is diagnosed with ovarian cancer.

Clinical Implications

Somatic Testing

Somatic testing for BRCA1/BRCA2 is available for all patients with a known high-grade serous ovarian cancer. Low-grade serous tumours do not require BRCA testing when the diagnosis has been confirmed by a specialist gynaecological cancer histopathologist.

Somatic testing is used to find predictors that may impact treatment. Certain genes found in cancerous tumours, such as homologous recombination deficiency (HRD) can be used to predict a patient's response to a type of therapy like PARP inhibitors. Microsatellite instability (MSI) is another mutation that might appear when undergoing tumour testing. MSI is more commonly useful with endometrial cancer, but if it is found in ovarian cancer patients, it can help predict responses to immunotherapy.

If, during tumour testing, a pathogenic variant is identified in a gene that is known to be associated with ovarian cancer predisposition (such as BRCA1/BRCA2), then germline testing for the same variant, if it has not already been

undertaken, is appropriate to determine if it is of germline origin.

Somatic testing for NTRK1, NTRK2 and NTRK3 fusion genes is available for metastatic ovarian cancer patients as a biomarker for treatment with an NTRK inhibitor when all other approved lines of treatment have been exhausted.

Germline Testing

All women with high-grade non-mucinous epithelial ovarian cancer (at any age) are eligible for germline testing of a number of genes associated with ovarian cancer susceptibility as part of a multigene panel. At present, the panel includes BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BRIP1, MLH1, MSH2 and MSH6 genes [23, 24]. Both germline and somatic testing should be undertaken in parallel to maximise variant identification.

Survival from ovarian cancer is improved in women who have a BRCA1/BRCA2 mutation compared with those who do not have a mutation. BRCA1/BRCA2-associated OC may also be more sensitive to chemotherapeutic agents, particularly DNA damage-inducing agents. Carboplatin, for example, induces double-stranded DNA breaks. Cancer cells that lack the correct function of BRCA proteins cannot efficiently repair these DNA breaks and are, therefore, more sensitive to DNA damage.

Germline as well as somatic BRCA mutated OC have been shown to benefit from Poly (ADP-ribose) polymerase inhibitors (PARP-i) therapy with improved progression free survival in both first line and recurrent settings [25, 26]. Knowledge of BRCA1/BRCA2 mutation status is significant to the patient and clinician in gaining a better understanding of the likely prognosis and in selecting the most effective therapeutic options. It is equally important to identify women who do not have a BRCA1/BRCA2 mutation as this group of women are least likely to benefit from PARP inhibitors and should therefore be considered for studies of novel therapies/combinations going forward.

HRD Testing

BRCA1/BRCA2 genes code proteins which are required in the homologous recombination repair (HRR) pathway of double stranded DNA breaks. PARP (poly ADP ribose polymerase) is an essential component of single-strand DNA repair. Inhibition of PARP leads to more double strand breaks and prevents HRR deficient (HRD) tumour cells from surviving chemotherapy induced DNA damage [27]. HRD may occur due to a large number of genes in the HRR pathway, including RAD51C, RAD51D, BRIP1 and PALB2. Tumours that are HRD deficient regardless if the HRD deficiency is inherited or sporadic are more susceptible to systemic therapy with 'PARP inhibitor' (PARPi) and platinum agents. Approximately 50% of high grade serous OC (HGSOC) are characterised by HRD.

Along with prognostic and treatment insights, HRD testing can also identify a person's family members' risk of getting ovarian cancer by detecting germline mutations of BRCA1/BRCA2 genes. It can similarly help identify ovarian cancer patients who are at risk for other cancers.

Case 3: BRCA 2 Mutation in Family

Age, Parity, PS	25 years old, P0 + 0, PS- 0
Clinical presentation	Presented for genetic counselling due to family history
Family history	History of high grade serous ovarian cancer stage 3-C in mother's older sister 2 years back (62 years, BRCA2 positive germline mutation) History of breast cancer (triple negative) in mother's younger sister (66 years); BRCA unknown, underwent surgery + chemotherapy History of renal cell cancer in mother's brother (60 years); underwent surgery History of cancer in both great grandparents (maternal)

This is a 25-year-old nulliparous patient with multiple family members with BRCA germline mutation positive cancers. A person who meet

criteria for BRCA1/BRCA2 testing, should be referred for risk assessment and pre-test genetic counselling, followed by determination of family status. Indications for testing, as well as the interpretation of results, should be done with the guidance of a genetic counsellor, geneticist or other health professional with expertise in genetics. If a familial BRCA1/BRCA2 pathogenic variant is known, the person should undergo genetic testing for that specific variant. If no familial BRCA1/BRCA2 variant is known, comprehensive BRCA1/BRCA2 testing or multigene testing for the hereditary breast and ovarian cancers panel should be considered.

Women with a BRCA1 mutation have a lifetime risk of ovarian cancer of up to 39% and of breast cancer of up to 65% by age 70 years. Risks of ovarian and breast cancers in women by age 70 years among BRCA2 carriers are reported to be up to 11% and 45% respectively [28]. The identification of BRCA1/BRCA2 mutation carriers has important clinical implications that pertain to risk-reduction interventions and characteristic features of BRCA-associated cancers.

Women with a BRCA1/BRCA2 mutation may consider several options for BC prevention. They can opt for MRI/mammography screening and chemoprevention with selective estrogen-receptor-modulators (e.g. Tamoxifen) to reduce their BC risk [29]. However, surgical prevention in the form of risk-reducing mastectomy (RRM) is the most effective option for reducing BC risk [30]. Several studies have demonstrated that RRM reduces the risk of breast cancer in women with BRCA1/BRCA2 mutations by approximately 90% [28, 30].

Effective preventive therapy options for this highly elevated risks of OC include screening, chemoprevention and risk reducing surgery. Women can also make lifestyle, contraceptive & reproductive choices impacting cancer risk including pre-natal or preimplantation genetic diagnosis (PGD) to prevent transmission to their children [31].

Screening for ovarian cancer has not been shown to be effective in a high risk population. Most of the studies in high risk cohorts used an annual surveillance strategy incorporating CA-125 and transvaginal ultrasound, with most cases detected at late stages [32]. Oral contraceptives (OCP) play an important role in chemoprevention. Use of OCP for 5 years is associated with a 50% decrease in ovarian cancer risk in women with BRCA1/2 mutations [33].

As there is no proven benefit to ovarian cancer screening, the mainstay recommendation for ovarian cancer prevention in women with BRCA1/BRCA2 mutations continues to be risk-reducing bilateral salpingo-oophorectomy (RRBSO). RRBSO in these women can usually be performed laparoscopically and should be undertaken in accordance with published protocols [34]. Multiple studies have demonstrated that RRBSO reduces ovarian cancer risk by 80% or more [35–37]. Furthermore, there is evidence that RRBSO prolongs survival. Studies have found a 60–76% reduction in overall mortality in BRCA1 and BRCA2 mutation carriers who have undergone RRBSO compared with those who have not [38, 39]. Timing of surgery is influenced by many factors including risk by age, childbearing plans, and risks of premature menopause.

If the above patient is identified with BRCA2 gene mutation then will be encouraged to complete her fertility needs and offered breast and ovarian cancer screening. There is a role for offering risk reducing surgery usually 10 years before the age of development of ovarian cancer. Patients with BRCA2 gene mutation develop ovarian cancer late usually after 50 years. As the family cohort, majority of the cancers developed in the 60 s, it is reasonable to offer RRBSO in the perimenopausal age group at 45–50 years.

RRBSO in premenopausal BRCA1 and BRCA2 mutation carriers also affects their breast cancer risk [37]. In BRCA1 mutation carriers the risk may decrease by as much as 56% and for women with a BRCA2 mutation by up to 46%, with the risk reduction being greatest if surgery is performed before 40 years of age [40]. It is therefore important that women are informed of this additional benefit.

Key Points

- Genetic assessment is crucial in identifying hereditary cancer syndromes identified in 5–10% of cancers.
- Careful counselling and communication is essential to help patients understand the implications of genetic testing.
- Genetic testing impacts treatment options and facilitates awareness and screening in other family members for prevention of genetic cancers
- Genetic testing allows patients to undertake cancer prevention program to prevent development of other sites of cancers.

References

1. Daniels MS, Lu KH. Genetic predisposition in gynecologic cancers. Semin Oncol. 2016;43(5):543–7. https://doi.org/10.1053/j.seminoncol.2016.08.005.
2. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105:569–74. https://doi.org/10.1097/01.AOG.0000154885.44002.ae.
3. Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. Cancer and Steroid Hormone Study Group. Cancer Epidemiol Biomark Prev. 1996;5(6):411–7.
4. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76:1–18. https://doi.org/10.1111/j.1399-0004.2009.01230.x.
5. Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. Fam Cancer. 2013;12(2):229–40.
6. Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15–25.
7. Crosbie EJ, Ryan NAJ, Arends MJ, Bosse T, Burn J, Cornes JM, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21(10):2390–400. https://doi.org/10.1038/s41436-019-0489-y.
8. Egoavil C, Alenda C, Castillejo A, et al. Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers. PLoS One. 2013;8(11):e79737.
9. Nice 2020. https://www.nice.org.uk/guidance/dg42/resources/testing-strategies-for-lynch-syndrome-in-people-with-endometrial-cancer-pdf-1053807829189.
10. Vasen HF, Moslein G, Alonso A, Bernstein I, Bertario L, Blanco I, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007;44(6):353–62.
11. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer. 2015;113:299–310.
12. Fountzilas E, Kotoula V, Pentheroudakis G, et al. Prognostic implications of mismatch repair deficiency in patients with nonmetastatic colorectal and endometrial cancer. ESMO Open. 2019;4(2):e000474. https://doi.org/10.1136/esmoopen-2018-000474.
13. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet. 2011;378(9809):2081–7.
14. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812–23.
15. Auranen A, Joutsiniemi T. A systematic review of gynecologic cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand. 2011;90(5):437–44. https://doi.org/10.1111/j.1600-0412.2011.01091.x.
16. Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer. 2002;94(6):1708–12.
17. Gerritzen LH, Hoogerbrugge N, Oei AL, Nagengast FM, van Ham MA, Massuger LF, et al. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. Familial Cancer. 2009;8(4):391–7.
18. Manchanda R, Saridogan E, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, et al. Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS). Arch Gynecol Obstet. 2012;286(6):1555–62.
19. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007;120(4):821–4.
20. Committee on Practice, B.-G. and O. Society of Gynecologic, ACOG Practice Bulletin No. 147: Lynch syndrome. Obstet Gynecol. 2014; 124(5):1042–1054.
21. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.

22. Systematic genetic testing for personalised ovarian cancer therapy (SIGNPOsT)2017 8.10.2017. https://www.isrctn.com/ISRCTN16988857?q=&filters=conditionCategory:Cancer&sort=&offset=4&totalResults=1950&page=1&pageSize=10&searchType=basic-search.
23. Chandrasekaran D, Manchanda R. Germline and somatic genetic testing in ovarian cancer patients. BJOG. 2018;125(11):1460. https://doi.org/10.1111/1471-0528.15225.
24. https://www.genomicseducation.hee.nhs.uk/genotes/in-the-clinic/presentation-patient-with-ovarian-cancer/.
25. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.
26. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15(8):852–61.
27. Schettini F, Giudici F, Bernocchi O, Sirico M, Corona SP, Giuliano M, et al. Poly (ADP-ribose) polymerase inhibitors in solid tumours: systematic review and meta-analysis. Eur J Cancer. 2021;149:134–52.
28. Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, Frost MH, Grant CS, Donohue JH, Woods JE, McDonnell SK, Vockley CW, Deffenbaugh A, Couch FJ, Jenkins RB. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93(21):1633–7.
29. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 2013;381(9880):1827–34.
30. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22(6):1055–62.
31. Menon U, Harper J, Sharma A, Fraser L, Burnell M, Elmasry K, et al. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod. 2007;22:1573–7.
32. Rosenthal AN, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol. 2013;31(1):49–57.
33. McLaughlin JR, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol. 2007;8(1):26–34.
34. Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG. 2011;118:814–24.
35. Finch AP, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32(15):1547–53.
36. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609–15.
37. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346:1616–22.
38. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–75.
39. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, et al. Mortality after bilateral salpingooophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006;7:223–9.
40. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 2005;23:7491–6.