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Radiation for Gynaecological Malignancies

Papa Dasari, Singhavajhala Vivekanandam and
Kandepadu Srinagesh Abhishek Raghava

Additional information is available at the end of the chapter

Abstract

Gynaecological malignancies are the most common cancers of women and they contribute to the significant amount of mortality. Women in developing countries are diagnosed in late stages and hence radiation is the common modality of therapy. Radiation is required in managing 80–90% of women with carcinoma cervix, 60% of women with endometrial cancer and 50% of women with carcinoma vulva. The stage of the disease is the most important factor in survival and counselling is essential to ensure complete therapy. Radiation is used as a primary therapy, adjuvant therapy, neo-adjuvant therapy and as palliation. The techniques include external beam radiation and brachytherapy or the combination of both. The newer techniques include IMRT-, IGRT- and PET-CT-guided therapies. Side effects/complications occur as acute during therapy, subacute within 3 months and chronic after 6 months. Management of these side effects is essential for increasing compliance of the patient so as to achieve high cure rates. Management of recurrent disease is a challenge and requires multidisciplinary approach involving Gynaecological Oncologist, Radiation Oncologist and Surgical Oncologist.

Keywords: radiotherapy, counselling, gynaecological malignancies, side effects, survival rates

1. Introduction

Radiation therapy in gynaecological malignancies is an essential component in achieving cure as well as palliation. Radiotherapy is required up to 80–90% of women with carcinoma cervix, 60% of women with endometrial carcinoma, 50% of women with carcinoma vulva, all women with vaginal cancer and 5% of women with ovarian cancer. The aim of radiotherapy is to kill the tumour cells without damaging the neighbouring normal tissues. The side effects of radiation can be severe and need to be recognized early to be treated effectively. Counselling of women suffering from

gynaecological malignancies who receive radiation is of great importance as adherence to treatment is one of the factors that influences survival rates. The most important part is the selection and categorization of women for radiation. The aim of this chapter is to appraise the readers about the burden of the gynaecological malignancies in a tertiary-care set up, counselling and selection criteria for radiation, methods of radiation and the side effects and the outcome.

1.1. Burden of gynaecological malignancies in tertiary care set up

Cancer is the first and foremost cause of death in developing countries and the second most common cause in developed countries. Genital tract malignancies are the most common cancers in women and the most common site affected is cervix followed by ovary and Uterine corpus [1]. The incidence of carcinoma cervix is 9 per 100,000 in developed countries as against 17.8 per 100,000 in developing countries. The mortality attributed to carcinoma cervix is 3.2 per 100,000 in developed regions when compared to 9.8 per 100,000 women in developing regions [2]. The cancer registry of our hospital recorded carcinoma cervix to be occurring in 70%, ovarian cancer in 20%, endometrial cancer in 9% and other cancers in 1% of cases in women. In India, every year 122,844 women were reported to be diagnosed with carcinoma cervix and 67,477 died of the disease and at present the trend of this malignancy is decreasing in incidence [3]. The incidence of carcinoma cervix has declined by 75% in developed countries [1].

2. Selection criteria for radiation

Staging of the malignant disease is the most important factor in determining therapy and while planning contraindications to radiation to be looked for and histopathological examination report is mandatory.

Contraindications for radiation: (1) Severe acute sepsis or febrile illness, (2) severe cancer cachexia, (3) myocardial infarction and (4) unequivocal histopathological report. Though there are no absolute contraindications, radiation is not the preferred therapy for radio-insensitive tumours like fibrosarcoma, leiomyosarcoma and melanoma.

Carcinoma cervix: The most common histopathological type is squamous cell carcinoma. The incidence of adenocarcinoma is on the rise contributing to as much as 25% [4]. In spite of the availability of screening tests in the modern era, as high as 85% are still presenting in late stage. Adherence to therapy is poor as it was reported that only 38.8% complete radiotherapy [5]. Pre-therapy staging is based on clinical examination and imaging findings. Recently, imaging techniques are playing a great role in planning therapy even though traditionally staging is done by clinical examination.

Role of imaging in staging:

- The accuracy of CT in staging carcinoma cervix is 63–88%. The sensitivity and specificity of CT in detecting pelvic lymph node involvement is shown in (**Table 1**)

- MRI distinguishes early from advanced disease, thereby stratifying patients for surgery and chemoradiation.

- MRI is used to assess cervical stromal invasion and extra-uterine extension and for assessing proximal extension of cervical tumour in young women with early-stage disease for the feasibility of fertility-preserving surgery [6].

- PET has sensitivity of 75% and specificity of 96% for the detection of pelvic lymphadenopathy and sensitivity of 100% and specificity of 99% for the detection of para-aortic lymphadenopathy. Its use has been increased, combined with CT, in the detection of nodal disease for locally advanced disease (>IB) [3, 5]. For early stage disease, the sensitivity and specificity of PET CT were about 73% and 97%, respectively.

- Grigsby et al. compared CT and FDG-PET scanning for lymph node staging in 101 patients with carcinoma of the cervix. CT detected enlarged pelvic lymph nodes and para-aortic lymph nodes in 20 and 7 patients, respectively, whereas PET detected abnormal FDG uptake in pelvic lymph nodes in 67, in para-aortic lymph nodes in 21 and in supraclavicular lymph nodes in 8. Based on para-aortic lymph node status, the 2-year progression-free survival rate was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive patients and 14% in CT-positive and PET-positive patients [7].

Survival rates are shown in **Table 2**.

CT	Sensitivity (%)	Specificity (%)
Pelvic + para-aortic lymph nodes	44	93
Para-aortic lymph nodes	67	100

Table 1. Sensitivity and specificity of CT.

Radiotherapy is advocated in the following situations:

(1) All stages especially when the woman is not fit for surgery or refuses surgery

(2) Following radical hysterectomy with positive pelvic lymph nodes

(3) Stages IIB to IV B

(4) Fertility sparing surgery which revealed a focus of positive lymph nodal metastasis

(5) Advanced stage carcinoma cervix following termination of pregnancy

(6) Persistent or recurrent disease

2.1. Carcinoma endometrium/Uterine Corpus

Carcinoma endometrium is the most common cancer of the uterus and its incidence is increasing. The median age is 63 years and more than 90% belong to 50 years of age or more and 25% occur before pre-menopause. More than 75% are diagnosed in Stage I as the most common symptom is abnormal or postmenopausal bleeding. Survival rates are more than 75%. Adenocarcinoma is the most common type with good prognosis, but it is relatively radioresistant.

S. no.	Stage (FIGO)	TNM (AJCC)	Survival rates (5-year observed rates)
	Stage 0		93%
1	Stage I A1	(T1a1, N0, M0	93%
2	Stage I A1	(T1a2, N0, M0)	
3	Stage I B	(T1b, N0, M0)	80%
4	Stage B 1	(T1b1, N0, M0)	
5	Stagve I B2	(T1b2, N0, M0)	
	Stage II	(T2, N0, M0)	63%
6	Stage II A	(T2a, N0, M0)	
7	Stage II A1	(T2a1, N0, M0)	
8	Stage II A2	(T2a2, N0, M0)	
9	Stage 2 B	(T2b, N0, M0)	58%
	Stage III	(T3, N0, M0)	
10	Stage III A	(T3a, N0, M0	35%
11	Stage III B	T3b, N0, M0; OR T1-T3, N1, M0) Hydronephrosis	32%
	Stage IV		
12	Stage IV A	(T4, N0, M0)	16%
13	Stage IV B	(any T, any N, M1)	15%

Table 2. Staging grouping of carcinoma cervix.

HPE grading:

Gx = Grade cannot be assessed

Grade 1 = Tumour cells are well-differentiated

Grade2 = Tumour cells are moderately differentiated

Grade 3 = Tumour cells are poorly differentiated

The histopathological types are as follows:

1. Endometroid adenocarcinoma (secretory, ciliated, papillary)

2. Adenocarcinoma with squamous differentiation

3. Adenoacanthoma (benign squamous component)

4. Adenosquamous carcinoma (malignant squamous component)

5. Papillary serous carcinoma

6. Clear cell adenocarcinoma

7. Carcinosarcoma/malignant mixed mullerian tumour

8. Uterine sarcomas

9. Mucinous tumours

10. Undifferentiated.

Staging of endometrial carcinoma with survival rates is shown in **Table 3**. Radiotherapy is also indicated in Stage I as per risk stratification.

TNM	FIGO stages	Surgico-pathological findings	Endometrial adenocarcinoma; 5-year survival	Endometrial carcinosarcoma; 5-year survival
Tx		Primary tumour cannot be assessed		
T0		No evidence of primary tumour		
Tis		Carcinoma *in situ* (Pre-invasive carcinoma)		
T1	**I**	**Tumour confined to Corpus**	88–75%	70%
T1 a	IA	Tumour limited to endometrium or Less than a half of endometrium is involved		
T1 b	IB	Tumour invasion of half or more than half of myometrium	f	
T2	**II**	**Tumour invades stroma of cervix and confined to uterus**	69%	45%
T3 a	**III A**	**Tumour involvement of serosa and/or adnexa (direct extension or metastasis)**	58–47%	30%
T3 b	III B	Vaginal involvement or parametrial involvement (direct extension or metastasis)		
	III C	Metastasis to pelvic and/or para-aortic lymph nodes		
	III C1	Pelvic lymph node metastasis		
	III C2	Para-aortic lymph node metastasis		
	IV	**Tumour invades bladder mucosa and/or bowel mucosa and/or distant metastasis**	17–15%	15%
T4	IV A	Bladder mucosa and Bowel mucosa are involved by tumour but no distant metastasis Bullous oedema is not considered as involvement		
	IV B	Distant metastasis; Lymph nodes, Lungs, bones Upper abdomen omentum; liver		

Note: T = denotes extent of the tumour; N = designates whether cancer has spread to the lymph nodes; M = denotes distant metastasis.

Nx = Spread to nearby lymph nodes cannot be assessed; N0 = no spread to nearby lymph nodes; N1 = spread to pelvic lymph nodes; N2 = spread to para-aortic lymph nodes.

Lymph node involvement: Stage I A-5%, Stage I B-10%; Stage I C-15%; Stage II-20% and Stage III-55%.

Distant spread: M0 = there is no spread to distant lymph nodes, organs and tissues; M1 = spread to distant lymph nodes, upper abdomen, omentum, other organs, liver, lung.

Table 3. TNM classification and FIGO staging [8].

Stage I low risk includes Stage I A grade 1 and 2 endometroid adenocarcinoma without or with minimal myometrial invasion.

Stage I intermediate-risk group includes Stage I with grade 1 or 2 adenocarcinoma with >50% myometrial invasion or grade 3 adenocarcinoma with superficial invasion and with extensive lymphovascular involvement

High-risk endometrial cancer includes Stage II with deep cervical stromal involvement and Stage III and IV disease.

2.2. Picture of USG and gross specimen of endometrial carcinoma (Figure 1)

Vulval and vaginal cancer:

A. Vulval carcinoma: Most common after 65 years of age but recently the incidence of carcinoma vulva in the age group between 40 and 49 years is reported to have been doubled. Its incidence is 1.3/100,000 women. Pathological types: Squamous cell carcinoma—90%; others include malignant melanoma, Paget's disease, Bartholin gland tumours, adenocarcinoma and basal cell carcinoma. Local recurrence is common when there is lymphovascular involvement, when the growth is of infiltrative type and when prominent fibromyxoid tumour is present at the edge of resected margins [9]. Gross picture of carcinoma vulva is shown in **Figure 2**.

Primary modality of therapy is surgical excision and groin lymph node dissection. Survival rates with staging are shown in **Table 4**.

Selection criteria for radiation:

Primary radiotherapy is suggested in women:

- When optimal surgical therapy is not possible.

- When Ulcerated groin nodes. Radiotherapy is followed by surgery or surgery followed by radiotherapy. However, surgery following radiation is associated with high morbidity.

Adjuvant radiotherapy is advised to groin and pelvic nodes in the following situations
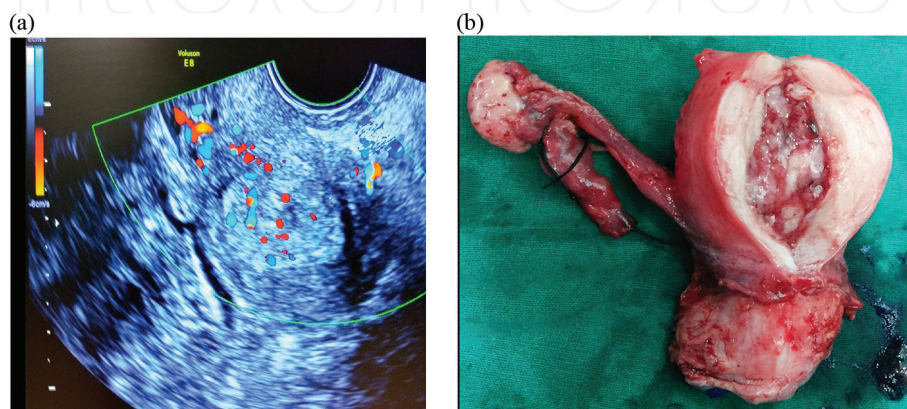

Figure 1. (**A**) USG (TVS) picture of endometrial carcinoma showing increased endometrial thickness and increased vascularity and (**B**) picture of same uterus (panel A) as gross specimen showing endometrial carcinoma in the cavity.

Figure 2. Cauliflower type of growth on the vulva.

(1) When one or two nodes show the spread either microscopic or extra capsular.

(2) When the resected margins are involved.

Pre-operative radiotherapy is advocated to preserve anal sphincter function when the tumour is close to the anal sphincter. Radiotherapy may also be combined with chemotherapy. Chemo-RT may increase the morbidity, especially skin toxicity.

Recurrence is very common in vulvar cancer and it varies from 15 to 33%. The sites of recurrence can be vulva itself (69.5%), groin nodes (24.3%) and distant sites (18.5%).

Stage grouping	Explanation	Survival rates (%)
Stage 0 (Tis,N0, M0)	Carcinoma *in situ*(only vaginal epithelium is involved)	84
Stage I (T1, N0, M0)	Cancer-confined vagina; no spread to lymph nodes/ distant sites	
Stage II (T2, No,M0)	Cancer invades the connective tissue below vagina No spread to lymph nodes and distant sites	
Stage III (T3, N0/1,M0) or (T1,/T2,N1, M0)	Spread of cancer to pelvic wall but not to lymph nodes or distant sites Or spread to lateral pelvic wall and/to lymph nodes pelvic or inguinal Not spread to distant sites	75
Stage IVA (T4, N0/N1,M0)	Cancer spread to rectum/bladder Lymph nodes may or may not have been involved No distant metastasis	57
Stage IV B (Any T, Any N, M1)	Cancer involves pelvic organs and spread to distant sites like lungs and liver, bone, etc.	

Note: Five-year survival rates for all stages together are reported as 50%; for squamous cell carcinoma 50%;for adenocarcinoma 60% and malignant melanoma 30%.

Table 4. FIGO and AJCC stage grouping and survival; carcinoma vulva.

B   Vaginal carcinoma: Vaginal cancer is rarely encountered and its incidence is reported to be 1 in 11,000 and ocxcurs in women more than 70 years of age and only 15% occur in women less than 40 years. Presenting symptoms are usually abnormal discharge, bleeding per vaginum, post-coital bleeding and mass per vaginum. Symptoms during late stages include constipation, pelvic pain and difficulty in micturition. Confirmation of diagnosis is by speculum examination demonstrating a cervix free of disease and growth in the vagina. Biopsy determines the type of cancer. If the growth involves cervix and vagina, it is classified under cervical cancer. If it involves vagina and vulva, it is classified as vulvar cancer. The most common pathological type is squamous cell carcinoma (70%); and others include adenocarcinoma (15%), melanoma (9%), sarcoma (4%) and miscellaneous [10].

3. Counselling for radiation

Counselling prior to radiotherapy is of utmost importance because of three reasons:

(1) To make the patient understand the process through which she would be going, i.e. the technique, the duration of therapy and the possible side effects and their significance and management.

(2) To make her compliant and complete the therapy for curative purposes or palliative purposes and follow-up for further therapy like surgery or chemotherapy and also the possibility or chances of recurrence.

(3) To help the patient to make informed decision and consent for the process.

Informed consent: [11]

Informed consent is to be taken by the radiotherapy counsellor/radiotherapy physician and it should include the diagnosis and stage of the disease, name of the procedure or treatment like external radiotherapy or brachytherapy or radio-isotope treatment, site of the body where radiation would be delivered and Whether the procedure is done under sedation, local/regional/general anaesthesia. The duration of therapy and the proposed sessions of therapy and whether it is for curative purpose or for palliative purpose is to be stated and signed by the concerned health professional involved in the care of the woman. The most common acute side effects and late side effects should be mentioned in the document signed by the health professional. An information leaflet to the patient in the language known to her or relatives would be desirable and is of great benefit.

The second part of the consent form should include statement that the patient has understood the benefits of the therapy, the short-term and long-term side effects that can occur and has the opportunity to ask questions and read the management protocol. The statement should also include the liberty of the patient to ask to stop the treatment at any time during the therapy after understanding the consequences of the same. A separate statement to be obtained from the reproductive aged women that she is not pregnant at this time of initiating the therapy

and would not plan to become pregnant during the course of therapy and she would inform the treating physician in case of such occurrence.

A statement for storing the data of the patient and its usage for the future purpose like research also can be included in this consent form.

Written consent would be obtained once prior to the procedure and at each session of treatment a verbal consent would be taken and this statement also to be included in the written consent form and to be signed and dated by the individual concerned.

In case of mental disease incapacitating the patient, a responsible attendant should be involved in the counselling process and in consenting in a similar way.

3.1. Survival rates

It is important to appraise the women and the relatives regarding prognosis and survival in addition to side effects whenever therapy is instituted. Though survival depends on many factors like age at the development of the malignancy, type of the tissue involved for example, cervix or endometrium or adnexa, histopathological type, modality of therapy, complications of therapy, compliance to therapy, associated co-morbidities and the chance for recurrence, the most important factor is found to be the stage of the disease. In other words, spread of the cancerous tissue is the most important factor that is used to prognosticate and explain the modality of therapy and its outcomes like overall survival. Survival rates are expressed variously and the standard way is to express in terms of 5-year survival. The survival rates for carcinoma cervix, endometrium and vulva are shown in **Tables 2–4**, respectively, and these should guide the clinician to explain the patient while undertaking counselling.

For carcinoma cervix, the survival rates reported in India include 47.7% in Mumbai-based registry in North India and 38% in Bangalore-based registry from South India. The 5-year survival rate for recurrent disease is reported to be between 30–60% and the main modality of treatment for recurrence being surgery. The prognosis is better if the recurrence occurs after 6 months of initial cure and the size of the recurrence is less than 3 cm [12].

4. Radiation therapy

Radiation therapy can be delivered as

(1) Primary radiotherapy

(2) Adjuvant radiotherapy

(3) Neoadjuvant radiotherapy

(4) Palliative radiotherapy

Primary radiotherapy: Primary radiotherapy involves the use of radiation therapy as the only modality of treatment either alone or in combination with chemotherapy which is used as a radiation sensitizer. Primary radiotherapy is used in the following situations: (1) women with unresectable, locally advanced disease; (2) women with resectable disease in whom the risk of surgical morbidity is unacceptably high and (3) women with medical risk factors that contraindicate primary surgical therapy.

Adjuvant radiotherapy: Early stage lesions of the lower genitourinary tract can be treated surgically if resection can be accomplished with adequate negative margins and acceptable morbidity. Post-operative radiotherapy/adjuvant radiotherapy is reserved for cases in which histopathologic analysis of the removed specimen reveals features suggesting a high risk of local recurrence.

Neoadjuvant radiotherapy: In advanced stage disease, sometimes neoadjuvant radiation is used before surgery to render an inoperable tumour operable and for preserving the organ.

Palliative radiotherapy: For women with distant metastatic disease at presentation, cure is unlikely and the aim of the treatment is to improve the quality of life. However, palliative radiotherapy is frequently used to palliate the symptoms of a painful bone metastasis, relieve features of raised intracranial tension in brain metastasis and relieve dyspnoea in superior vena cava obstruction.

4.1. Techniques of radiation

The two main modalities of irradiation are teletherapy (external beam radiation) and brachytherapy. External beam irradiation is used to treat the whole pelvis including the uterus, cervix fallopian tubes and ovaries, parametria and the regional nodes. A linear accelerator is used to deliver mega voltage photons to treat the whole pelvis. Gamma rays from a cobalt-60 machine are also used to deliver radiation.

Brachytherapy: In this modality, source of radiation is placed inside the body as close to the tumour as possible. It usually consists of the placement of intrauterine and vaginal applicators. These are then loaded with the source of radiation. Cesium-137 (^{137}Cs) is the most popular low-dose rate (LDR) source and Iridium-192 (^{192}Ir) is the most common high-dose rate source (HDR). Treatment with HDR is usually completed in a few minutes, whereas an LDR source takes 1 or 2 days to complete the treatment.

4.2. Technique of external beam radiation

External beam radiation in the treatment of carcinoma cervix aims at treating the whole pelvis. Whole pelvis involves treating the pelvic organs uterus, adnexa and upper third of vagina, parametrial tissues (cardinal, uterosacral and pubo-cervical ligaments) and pelvic lymph nodes (internal and external iliac, obturator and pre-sacral lymph nodes). Traditionally, the whole pelvis is treated with four fields—anterior-posterior portals and two lateral fields (**Figure 3A** and **B**)]. Upper border is placed at L4-L5 interspace to adequately cover the external iliac and lower common iliacs. The lower border is kept 3 cm below the lower extent of the tumour or lower border of obturator foramen if the vagina is not involved by the tumour.
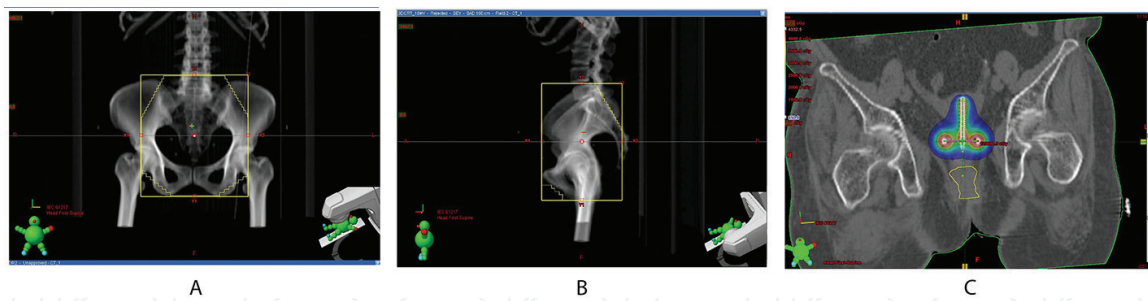
Figure 3. (**A**) Anterior field borders, (**B**) lateral field borders, and (**C**) HDR brachytherapy dose distribution [pear-shaped].

The lateral borders are kept 2 cm lateral to the pelvic brim in order to adequately cover the iliac nodes. The upper and lower borders of the lateral fields correspond with those of the AP-PA fields. The anterior border is kept at the anterior border of the pubic symphysis and the posterior border is placed to cover the entire sacrum. High-energy beams of the range of 6–15MV are used to deliver radiation. Dose of external beam radiation is 46 Gy in 23 fractions, 200 cGy per fraction and one fraction a day 5 days a week. The dose distribution of four field box plan is shown in **Figure 4A** and bladder and rectum contours are shown in **Figure 4B**.
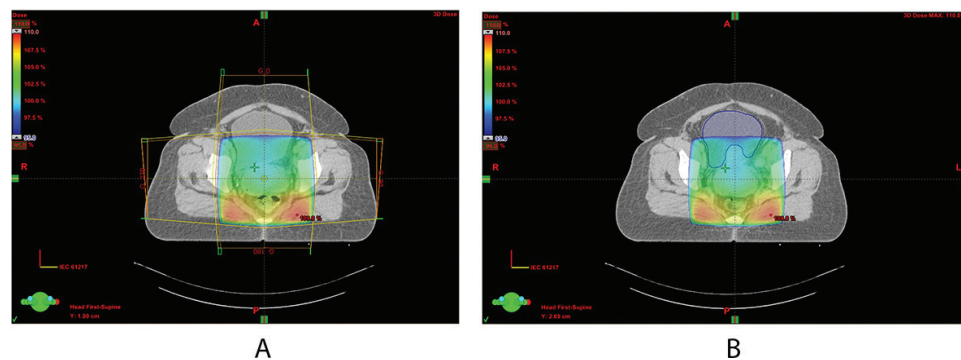

Figure 4. (**A**) 3DCRT plan showing 95% coverage with four fields and (**B**) dose distribution of four field box plan showing 95% coverage with bladder and rectal contours.

4.3. 3D planning techniques

- CT scan is taken with patient supine with arms on the chest, knees and lower legs immobilized, and anterior and lateral tattoos marked with radio-opaque material aligned with lasers to prevent lateral rotation.

- Clinical examination is made in the treatment position and inferior extent of tumour in the vagina marked with radio-opaque material.

- Patients will be instructed to maintain a constant bladder filling—'comfortably full'—and instructions will be given to empty the bladder two hours before simulation and to drink one litre of water mixed with 60 ml of Gastrovideo oral contrast. Ondansetron 8 mg or domperidone 10 mg will be given if needed. To delineate large bowel, instructions will be given to drink one litre

of water mixed with 60 ml of Gastrovideo oral contrast within 1 hour, 24 hours prior to simulation. Only liquid diet will be allowed after that, till simulation. Domperidone 10 mg will be given.

- CT Scan is taken from the first lumbar vertebra to 5 cm beyond the vaginal introitus. Intravenous contrast is used to outline pelvic blood vessels to be used as surrogates for pelvic nodes in CTV delineation.

- *Target volume definition*

    While defining clinical target volume (CTV), gross tumour volume (GTV) along with cervix, uterine volume is added. Entire uterus is delineated including the fundus. CTV-T includes the primary GTV-T with potential microscopic spread to cervix, uterus, parametrial tissues, upper vagina, and broad and proximal utero-sacral ligaments. If posterior extension of cervical tumour is present, the entire utero-sacral ligaments and upper pre-sacral nodes are included. CTV-N includes the pelvic lymph nodes, i.e. obturator, internal, external and common iliac, and upper pre-sacral nodes. These are delineated by identifying contrast-enhanced pelvic blood vessels on each CT scan and using a 7 mm margin to create a 3D CTV.A typical CTV to PTV margin of 10 mm is used around the CTV-T to allow for organ motion of cervix and uterus and measured set-up uncertainties. For CTV-N, organ motion occurs to a lesser extent and a 7–10 mm CTV to PTV margin is typically sufficient for set-up variations. The contours of GTV, bladder and rectum are shown in (**Figure 5**).
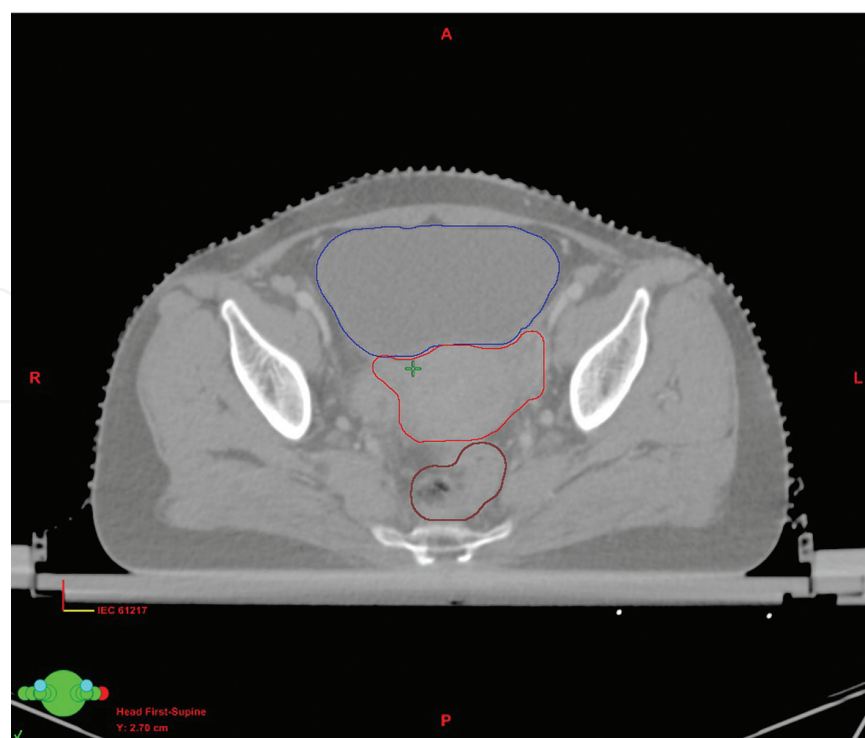

Figure 5. Planning CT showing contours of GTV, bladder and rectum.

4.4. Technique of brachytherapy

The high tolerance of the uterus and vagina make it ideally suited for brachytherapy. In brachytherapy, sealed radioactive sources are used to deliver radiation at short distances. It is possible to deliver a high dose locally to the tumour with a rapid dose fall-off from the surrounding normal tissues. The commonly used isotope for high-dose rate brachytherapy includes Iridium 192 and Cobalt 60. Caesium 137 is used for low-dose rate brachytherapy. Uterine tandem is inserted into the length of which depends on the length of the uterus. Two ovoids are placed in the fornices and the vagina is packed with gauze. This decreases the dose to the rectum and bladder. Using an after loading technique, the source is introduced into the ovoids and tandem. The dwell time and dwell position is calculated so that the desired dose to Point A is achieved. In JIPMER, the dose prescribed to Point A is 8.5 Gy × 3 using Iridium 192. The classical isodose for intra-cavitary brachytherapy of carcinoma cervix is pear-shaped (**Figure 3C**).

4.5. JIPMER radiotherapy protocol for carcinoma cervix—summary (Table 5)

The standard treatment for women with FIGO IB2, IIA, IIB, IIIA, IIIB and IVA disease is concurrent chemo-radiation. Surgery is not preferred because of the increased risk of positive margins and positive nodes. Concurrent chemo-radiotherapy is preferred to radiation alone since the addition of concurrent chemotherapy confers an overall survival advantage [RR risk reduction is 29%] [13]. Platinum-based chemotherapy is preferred over non-platinum-based chemotherapy since there is more benefit with platinum-based compounds (5FU). The hazard ratio (HR) for platinum is 0.70 (95% confidence interval, CI 0.61–0.80; $p < 0.0001$) compared to 0.81 (95% CI 0.56–1.16; $p = 0.20$) for non-platinum-based chemotherapy. 118 chemoradiation with cisplatin alone is comparable to chemo-radiation with cisplatin/5-fluorouracil. However, concurrent chemo-radiation for treatment of cervical cancer is associated with increased acute toxicities specifically haematological and gastro-intestinal toxicity [13].

4.6. RT for carcinoma cervix in special situations

(1) Acute haemorrhage

Women presenting with acute episode of hemorrhage need to be hospitalised and stabilised with blood transfusion and vaginal packing

Broad spectrum antibiotics and antifibrinolytics are to be started.

Haemostatic RT—Whole Pelvis EBRT-2 Gy/# standard fractionation as per stage-wise treatment protocol. If bleeding persists, brachytherapy with ovoids will be considered.

(2) Pregnancy: First and second trimester pregnant women are managed by medical termination of pregnancy as appropriate for gestational age by medical methods .This is followed by stage-wise treatment after 2 weeks

Third trimester—Pregnancy is continued till 34 weeks with fetal monitoring and institution of steroids for fetal lung maturity followed by elective caesarean section. Stage-wise treatment is undertaken after 4 to 6 weeks of caesarean section.

(3) Utero-vaginal prolapse: Manual reduction during RT if possible; procedentia—prolapse reduction under anaesthesia and labial stitching followed by RT.

(4) HIV:HAART—Highly active anti-retroviral treatment

   CD4 > 200 cells/ml—Stage-wise treatment with radiotherapy + chemotherapy

   CD4 50–200 cells/ml—Stage-wise treatment with radiotherapy

   CD4 < 50 cells/ml—palliation of symptoms

   Use of universal aseptic precautions during P/V examination.

Stage	EBRT	ICBT-HDR	BED	LQED at 2 Gy/#	Recommended dose to point A
IA1	0	7 Gy× 6# Ovoid &tandem	71.4	59.5	70–80 Gy
IA2, IB1, IIA1, IB2, IIA2	46 Gy/23# WP	8.5 Gy× 3# Ovoid &tandem or ring &tandem	102.4	85.3	80–85 Gy
IIB	45 Gy/20# WP or 46 Gy/23# WP	8.5 Gy× 3# Ring &tandem or ovoid &tandem	102.3 102.4	85.2 85.3	>85 Gy
IIIA	46 Gy/23# WP 4 Gy/2#PM boost 6 Gy/3# PO	6 Gy× 3# linear applicator	96	80	85–90 Gy
IIIB <2/3 of upper vaginal involvement	45 Gy/20# WP 4.5 Gy/2# PM-Boost Or 46 Gy/23# WP 4 Gy/2# PM-Boost	8.5 Gy× 3# Ring &tandem or Ovoid &tandem	109.8 107.2	89.8 89.3	85–90 Gy
IIIB >2/3 of upper vaginal involvement	46 Gy/23# WP 4 Gy/2#PM boost 6 Gy/3# PO	6 Gy× 3# Linear applicator	96	80	85–90 Gy
IVA (Poor performance status),	30–39 Gy/10–13# (Palliative RT to gross disease)	No brachytherapy	39–50.7	32.5–42.25	
Post-op	46 Gy/23# WP	8 Gy× 2# Vault brachytherapy	84	70	

Table 5. JIPMER radiotherapy protocol for carcinoma cervix—summary.

4.7. Incidentally diagnosed carcinoma cervix after simple hysterectomy/Stump carcinoma after subtotal hysterectomy for benign disease

- Pathological review—no LVSI—Stage I A1— follow-up

- Stage IA1 with LVSI (or) > Stage IA2 Negative margins, negative imaging—pelvic RT + brachytherapy + chemotherapy

    (or)

    Complete parametrectomy + upper vaginectomy + pelvic lymph node dissection + PA LN sampling followed by adjuvant RT or chemo RT as per the above indications

- Positive margins, gross residual disease—if imaging negative for nodal disease—chemo RT, if imaging positive for nodal disease—consider for surgical debulking of grossly enlarged nodes followed by chemo RT.

4.8. Carcinoma of the endometrium protocol at JIPMER

History and physical examination; biopsy report confirmation of carcinoma and type of carcinoma:

- Haemogram

- Kidney function tests—blood urea, serum creatinine, serum electrolytes, creatinine clearance

- Liver function tests

- Random blood sugar

- Chest X-ray

- Ultrasonography—abdomen and pelvis

- HBs antigen

- HIV serology

- CECT/MRI abdomen and pelvis

- Cystoscopy and sigmoidoscopy as clinically indicated

4.9. The evidence present in treating endometrial cancer with radiotherapy

In women with Stage I intermediate-risk external beam pelvic radiotherapy reduces the local as well as vaginal recurrences. Vaginal brachytherapy alone also can achieve similar recurrence rates in this group of women. In women with intermediate- to high-risk group, the overall survival is also similar with external pelvic beam radiation and vaginal brachytherapy. The role of chemotherapy combined with radiation not well established.

5. Evidence-based recommendation ESMO-ESGO-ESTRO consensus [14] (Table 6)

5.1. Normal tissue tolerance

Organs at risk (OAR) in radiation therapy of endometrial cancer include the bladder, rectum, small intestine and the femoral heads.

Radiation therapy for endometrial cancer and tissue tolerance (**Table 7**).

EBRT for endometrial cancer: The technique almost similar as that of carcinoma cervix planning except that the AP/PA field upper border is placed at L5-S1 junction. The pelvis is treated with EBRT to 45–50 Gy in 25–28 daily fractions using 6–18 MV photon beams. The target volume is defined by GTV of the entire uterus in inoperable cases. CTV includes vaginal cuff, obturator nodes, external, internal and common iliac nodes. Planning target volume (PTV) is calculated as CTV plus 0.5–1 cm or ITV (internal target volume) plus 0.5 cm.

Brachytherapy delivers high dose to the vagina while minimizing dose to organs at risk. A vaginal cylinder of largest feasible diameter is the most common applicator used. The radiation is delivered with low-dose rate (LDR) or high-dose rate (HDR) radiotherapy. 50–60 Gy is the LDR prescription to the surface over 60–70 h when used alone. When combined with EBRT, the prescription dose is reduced to 25–30 Gy. The HDR dose prescriptions recommended by the American Brachytherapy Society (ABS) for adjuvant endometrial cancer is as follows. Suggested doses of HDR alone (**Table 8A**) and suggested doses of HDR to be used with 45 Gy EBRT for adjuvant endometrial cancer (**Table 8B**).

5.2. Carcinoma of the vulva

In patients with early stage vulval cancer with high risk features, radiation is commonly delivered following surgery. In patients with locally advanced tumours, surgery will result in unacceptable morbidity and poor cosmetic outcome. Radiotherapy in combination with concurrent chemotherapy is used for 'organ preservation' and cure. Apart from biopsy confirmation of vulval lesion, FNAC of clinically positive inguinal nodes is mandatory and all other investigations prior to RT as per other malignancies are undertaken.

Normal tissue tolerance: Organs at risk (OAR) in radiation therapy of vulvar cancer include the bladder, rectum, small intestine and the femoral head similar to that of endometrial cancer and the tolerance of vagina is <75–80 Gy.

5.3. RT planning techniques: simulation and field arrangements

- Photon energy of more than 6 MV is required for treatment. CT is required for measuring the depth of inguinal nodes. Patients are simulated with custom immobilizations. Supine, frog-leg positions are preferred to reduce the bolus effect from skin folds, with full bladders to reduce dose to small bowel.

- Radio-opaque markers should be used to delineate vulva tumour, scars, palpable lymph nodes, extent of vaginal involvement if present and anal verge.

- Borders of AP field should include superiorly from mid-sacroiliac joint to cover external and internal iliac nodes or L4-L5 level to cover the common iliac nodes if internal or external iliac nodes appear suspicious or positive.

- Inferiorly it should include the entire vulva or lower margin of the tumour (whichever is more caudal).

- Lateral border should include greater trochanter to cover the inguinal nodes in the AP field and 2 cm beyond the outermost point of the pelvic inlet on the PA field.

- *Narrow PA field*: Superior and inferior extent to same as that of wide AP field but lateral extent is farther off from femur-matching supplemental electron fields.

- Anterior electron fields to the lateral inguinal region matched with the exit PA field. Energy of the beam is selected depending on the CT depth of femoral vessels

- *Conedown: After 45 Gy to the pelvis, fields have to be reduced to include the* primary tumour and involved inguinal lymph nodes with 2–3 cm margin.

Risk group	Description	Recommended management
Low	Stage I endometroid, grade 1–2, <50% myometrial invasion, LVSI negative	The risk of recurrence after surgery alone is less than 5% No adjuvant treatment is recommended
Intermediate	Stage I endometroid, grade 1–2, >50% myometrial invasion, LVSI negative	Vaginal brachytherapy (PORTEC-2)
High-intermediate	Stage I endometroid, grade 3, <50% myometrial invasion, regardless of LVSI status Stage I endometroid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion	Node negative-brachytherapy **No surgical nodal staging:** Adjuvant EBRT recommended for LVSI unequivocally positive to decrease pelvic recurrence Adjuvant brachytherapy alone is recommended for grade 3 and LVSI negative to decrease vaginal recurrence
High	Stage I endometroid, grade 3, >50% myometrial invasion, regardless of LVSI status	**Surgical nodal staging performed, node negative:** Adjuvant EBRT with limited fields should be considered to decrease locoregional recurrence Adjuvant brachytherapy may be considered as an alternative Adjuvant systemic therapy is under investigation **No surgical nodal staging:** Adjuvant EBRT is recommended for pelvic control and relapse free survival Sequential adjuvant chemotherapy may be considered to improve PFS and CSS There is more evidence to support giving chemotherapy and EBRT in combination rather than either treatment modality alone
High	Stage II	**Surgical nodal staging performed, node negative:** Grade 1–2, LVSI negative: recommend vaginal brachytherapy to improve local control Grade 3 or LVSI unequivocally positive: Recommend limited field EBRT Consider brachytherapy boost Chemotherapy is under investigation **No surgical nodal staging:** EBRT is recommended Consider brachytherapy boost Grade 3 or LVSI unequivocally positive: sequential adjuvant chemotherapy should be considered

Risk group	Description	Recommended management
High	Stage III endometroid, no residual disease	EBRT is recommended IIIA: Chemotherapy and EBRT to be considered IIIB: Chemotherapy and EBRT to be considered IIIC1: Chemotherapy and EBRT to be considered IIIC2: Chemotherapy and extended field EBRT to be considered
High	Non-endometroid (serous or clear cell or undifferentiated carcinoma or carcinosarcoma	**Serous and clear cell after comprehensive staging:** Consider chemotherapy; clinical trials are encouraged Stage IA, LVSI negative: Consider vaginal brachytherapy only without chemotherapy – Stage ≥IB: EBRT may be considered in addition to chemotherapy, especially for node-positive disease **Carcinosarcoma and undifferentiated tumours:** Chemotherapy is recommended Consider EBRT; clinical trials are encouraged
Advanced	Stage III residual disease, Stage IVA	Palliative RT/Chemotherapy
Metastatic	Stage IVB	Palliative chemotherapy/RT/best supportive care

Note: The 5-year risk of recurrence is 2–10, 20–25 and 30 % for low risk, intermediate risk and high risk, respectively [15].

Table 6. Evidence-based recommendation ESMO-ESGO-ESTRO consensus [14].

OAR	Dose limitations
Bladder	V80 < 15%, V75 < 25%, V65 < 50%
Rectum	V50 < 50%, V60 < 35%, V65 < 25%, V75 <15%
Small intestine	V15 <120 cc, V45 < 195 cc
Femoral heads	Dmax < 40 Gy

Note: V = volume of tissue receiving n% of Gy.

Table 7. Radiation therapy for endometrial cancer and tissue tolerance.

Number of HDR fractions	Dose/fraction	Dose-specific point
3	7	0.5 cm depth
4	5.5	0.5 cm depth
5	4.7	0.5 cm depth
3	10.5	Vaginal surface
4	8.8	Vaginal surface
5	7.5	Vaginal surface

Table 8A. Suggested doses of HDR alone.

5.4. Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) improves conformality and eliminates matching problem between electrons and photons over 3DCRT (3D conformal radiation) for vulvar cancer.

Number of HDR fractions	Dose/fraction	Dose-specific point
2	5.5	0.5 cm depth
3	4	0.5 cm depth
2	8	Vaginal surface
3	6	Vaginal surface

Table 8B. Suggested doses of HDR to be used with 45 Gy EBRT for adjuvant endometrial cancer.

IMRT reduces the dose to bladder, rectum, small bowel and head of femur. Definitions of CTV and PTV in 3DCRT and IMRT are as follows: CTV should include 1-cm margin including the entire vulvar region and the bilateral external iliac, internal iliac and inguinofemoral nodes. PTV should include 1 cm margin around CTV.

5.5. Dose prescriptions (Table 9)

Carcinoma of the vagina: Colposcopy-directed biopsy of the cervix and vulva to rule out primary cervical and/or vulvar cancer is undertaken apart from other investigations prior to radiotherapy. In women with early and locally advanced vaginal cancer, radiation is often the sole treatment either alone or in combination with concurrent chemotherapy which is used as a radiation sensitizer. RT comprising both external beam irradiation and brachytherapy is the treatment of choice. Brachytherapy can be intra-cavitary or interstitial depending on the depth of invasion. Intra-cavitary brachytherapy is used to treat superficial lesions <5mm in depth from the vaginal surface. Interstitial brachytherapy is used to treat lesions involving >5mm of depth from the vaginal surface.

5.6. Radiotherapy for vaginal cancer (Table 10)

5.6.1. RT planning techniques simulation and field arrangements

- Patients are simulated in supine, frog-leg positions (to minimize the bolus effect from skin folds) with full bladders (to minimize the volume of small bowel in the radiation field), with custom immobilizations.

- CT scan will be taken from the first lumbar vertebra to 5 cm beyond the vaginal introitus, and anterior and lateral tattoos marked with radio-opaque material aligned with lasers to prevent lateral rotation.

5.6.2. AP/PA field

Superior border will be placed at L5-S1 and inferior border at 3–4 cm below the vaginal marker and lateral borders at 1.5–2cm of the true pelvic rim. If inguinal lymph nodes are to be treated, wide AP fields will be planned to cover inguinal regions with narrow posterior fields with 2:1 weighting.

Setting	Scenario	Dose (Gy)
Preoperative		45–50
Post-operative	Microscopic residual	50
	Extracapsular extension or node positive	55–60
	Gross residual	65–70
Definitive	Concurrent chemoradiation	60–65

Table 9. Dose prescriptions.

Stage	Therapy
Stage I	Brachytherapy alone or combined with EBRT
Stage II	EBRT to the primary and pelvic lymph nodes along with brachytherapy boost is recommended. If the parametria are involved, treatment should include parametrial boost
Stage III–IV A	EBRT to the primary and pelvic lymph nodes along with parametrial boost and brachytherapy boost, with concurrent chemotherapy is recommended

Table 10. Radiotherapy for vaginal cancer.

5.6.3. Dose prescriptions

EBRT dose of 46 Gy with brachytherapy dose of 25–30 Gy is recommended. EBRT boost to 64–70 Gy is used instead of brachytherapy for extensive lesions and those involving recto-vaginal septum.

5.6.4. Normal tissue tolerance

Organs at risk (OAR) in radiation therapy of vaginal cancer include the bladder, rectum, small intestine and the femoral heads **Table 11**.

5.7. Carcinoma of the ovary

The role of radiation is limited in carcinoma ovary. Whole-abdomen radiation has been used, but its popularity has waned because of the favourable toxicity profiles of the current chemotherapeutic regimens.

6. Newer modalities

Newer external radiation techniques, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic body radiotherapy (SBRT), proton therapy and PET-CT-guided radiation, have been tried in gynaecological cancers, but these require further validation.

OAR	Dose limitations
Bladder	V45 < 35%
Rectum	V30 < 60%
Small intestine	V15 <120 cc, V45 < 195 cc
Femoral heads	V30 < 15%

Note: Vn% = volume of tissue receiving *n*% of Gy.

Table 11. Tissue tolerance for vaginal RT.

6.1. Intensity-modulated radiation therapy (IMRT)

The technique of IMRT was developed using inverse planning. Intensity of the beam will be modulated spatially with the help of multileaf collimators. The advantage of IMRT lies in the reduction of amount of radiation dose received by small bowel and bone marrow. The use of IMRT is still under evaluation for intact cervix cases, but has been validated in the post-operative setting. Gandhi et al. reported the toxicities of pelvic radiotherapy in 44 patients, of which 22 received 3DCRT and 22 received IMRT. IMRT resulted in significant reduction of gastrointestinal toxicities with comparable clinical outcome. Patients who received IMRT had fewer grade 2 and grade 3 gastrointestinal toxicities as compared with 3DCRT [16]. Du et al. evaluated the dosimetry, efficacy and toxicity of IMRT in advanced cervical cancer. IMRT provided better target dose conformity and better sparing of small bowel, bladder and rectum. They concluded that IMRT resulted in improved dose distributions with significantly lower toxicities with comparable clinical outcome [17]. The dose distribution of IMRT is shown in **Figure 6**.
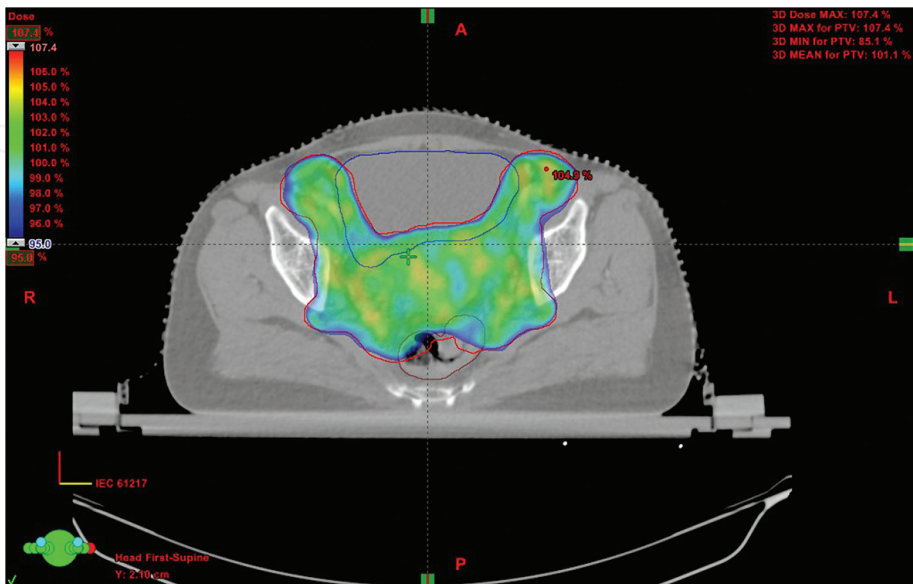

Figure 6. Dose distribution of IMRT showing 95% coverage.

6.2. Image-guided radiation therapy (IGRT)

The definition of IGRT, as given by the American College of Radiology and American Society of Radiation Oncology practice guidelines, is a procedure that refines the delivery of therapeutic radiation by applying image-based target relocalization to allow proper patient repositioning for the purpose of ensuring accurate treatment and minimizing the volume of normal tissue exposed to ionizing radiation [18]. It is particularly useful in cases with a large mobile uterus as seen in young women and with a concern regarding the position of the uterus in the planned radiation field.

6.3. Stereotactic body radiotherapy (SBRT)

SBRT delivers radiation with large fraction sizes using highly conformal treatment techniques. In isolated para-aortic node cases, it has been considered for a nodal boost. It should not be used as replacement for brachytherapy due to the significant increase in normal tissue doses with SBRT as compared with brachytherapy.

6.4. Proton therapy

The rationale for proton therapy lies in the improvement of therapeutic ratio by reducing the radiation dose to non-targeted tissues, thereby reducing toxicity and facilitating dose escalation to achieve increased tumour control. Proton therapy can offer the best way of sparing the small bowel and rectum and can contribute to significant decrease in acute and chronic toxicities in cervical cancer treatment.

6.5. Image-guided brachytherapy

Currently, image-guided adaptive brachytherapy in gynaecological malignancies is based on CT and MRI. Ultrasonography (USG) as an imaging modality for guidance is also being explored. Advantages of USG include easier availability, cost-effectiveness and small learning curve which makes it highly useful in developing countries. Limited availability and accessibility to CT and MRI prevented the early adoption of these promising techniques. Potter et al. reported the clinical outcome of 156 patients treated with image-guided brachytherapy. Ninety-seven percent of patients achieved complete remission with 3-year overall local control rates of 95%, 3-year overall cancer-specific survival rates of 74% and 3-year overall survival rates of 68%. They concluded that there is reduction in major morbidity and pelvic recurrence with the use of image-guided brachytherapy [19].

Side effects of pelvic radiation:

Radiation-induced side effects depend on the type of tissue, dosage and methods of delivery of radiation, and the manifestations can be acute and chronic. Acute side effects usually occur during or within the first 3 months of completing radiation. These include fatigue, skin irritation or redness of the skin and loose bowel movements discomfort when urinating.

Chronic side effects occur 3 months after completion of radiation. It includes skin changes like thinning of skin, radiation enteritis which manifest as loose stools and bleeding per rectum, cystitis, vaginal stenosis and intestinal obstruction and perforation are other uncommon side effects. Common late toxicities include vaginal stenosis/shortening, dryness, fibrosis, telangiectasia, atrophy of skin. Fracture of femoral neck has been implicated with osteoporosis and smoking. Avascular necrosis of the femoral head, though extremely rare, may also occur. Infection, lymphocyst formation and lymphoedema have been associated with groin radiation. Psychosocial consequences which are related to sexual function and body image may occur. With 200 Gy, the rate of tissue necrosis is less than 1% for cervical tissue and vagina is more sensitive with a tolerance of 100–140 Gy, beyond which necrosis is common. The complication of vesicovaginal fistula may result beyond a threshold of 150 Gy and rectovaginal fistula at 80 Gy [5].

Nutrition is important and should contain high protein. Plenty of oral fluids intake of more than 3 litre is necessary to avoid dehydration. When EBRT is employed, skin is the most commonly affected tissue. Avoiding soap and other irritants is important to avoid ulceration.

7. Follow-up and management of side effects

- Two months for the first year, 3 months for the next 2 years, 6 months for the next 2 years and then annually from 5 years.

- History of side effects and physical examination including pelvic and rectal examination and biopsy if recurrent growth.

- CT/MRI for all patients during the first year of follow-up. If cervix cannot be assessed, imaging will be done annually.

- Patient education regarding sexual health, vaginal dilator use, vaginal lubricants/moisturizers (oestrogen creams) is undertaken at each follow-up visit.

- Patients with fistula, who had complete response on follow-up, will be referred for fistula repair.

8. Treatment of recurrent carcinoma of cervix

- *After previous surgery*

Approximately 50% of patients with localized recurrences after surgery alone may be salvaged with radiation. EBRT (45–50 Gy) with concurrent chemotherapy followed by brachytherapy is recommended. If the tumour is inaccessible for brachytherapy, dose escalation with IMRT with at least 65–70 Gy may be attempted.

- *After definitive irradiation*

Important factors to be considered for re-irradiation are the time period between the two treatments, beam energy, volume and doses delivered in the initial treatment. EBRT for recurrent tumour is given to limited volumes (40–45 Gy, 1.8 Gy/fraction).

8.1. Treatment of recurrent carcinoma of endometrium

Radiation therapy can be used to treat small vaginal recurrences in patients who have not received prior radiation. EBRT (45–50 Gy) and brachytherapy are often combined.

8.2. Treatment of recurrent carcinoma of vagina

Lesions that recur after limited surgical procedures can be treated using radiation or more extensive surgery. Most patients have received prior EBRT and, thus, have options limited to surgery.

8.3. Treatment of recurrent carcinoma of vulva

If there is clinical local recurrence confined to vulva or clinical nodal recurrence, no prior RT, then EBRT with concurrent chemotherapy can be delivered. Doses range from 50.4 Gy in 1.8 Gy/# for adjuvant therapy to 59.4–64.8 Gy in 1.8 Gy/# for unresectable disease. Large nodes may be boosted to a dose of 70 Gy.

9. Conclusion

Radiation therapy in gynaecological malignancies involves multidisciplinary approach, careful planning and execution. Counselling is an essential part to increase compliance and to achieve high cure rates.

Author details

Papa Dasari[1],*, Singhavajhala Vivekanandam[2] and Kandepadu Srinagesh Abhishek Raghava[2]

*Address all correspondence to: dasaripapa@gmail.com

1 Department of Obstetrics and Gynaecology, JIPMER, Puducherry, India

2 Department of Radiotherapy, Regional Cancer Centre, JIPMER, Puducherry, India

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