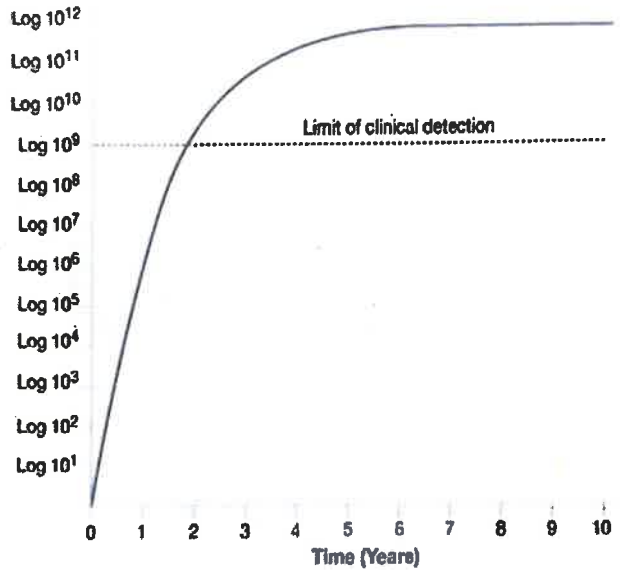
NEET SS OBG
GYNECOLOGIC ONCOLOGY

CONTENT

- Tumor vol is reduced by Sx or CTx and the remaining cells move from G0 to G1 phase.
- Log cell kill : Constant fraction of cells are killed.



During early stages of tumor expansion, growth is exponential, but with enlargement, tumor growth slows. Consequently, most tumors have completed their exponential growth phase at the time of clinical detection.

The Growth curve of tumor cells.

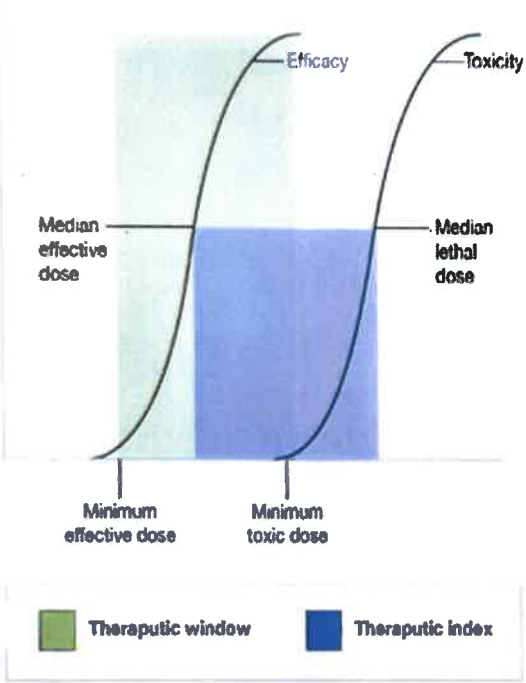
Uses of chemotherapy 00:23:52

Types of chemotherapy :

1. Induction chemotherapy.
   - Primary Rx.
   - Used in advanced malignancy & when there is no alternative Rx.
2. Adjuvant chemotherapy.
   - To destroy microscopic cells after primary tumor removed by Sx.
3. Neoadjuvant chemotherapy.
   - Used in advanced Ca.
   - Given prior to the surgery.
4. Maintenance (Consolidation) chemotherapy.
   - Given after treatment, to maintain prolonged duration of remission.
5. Salvage (Palliative) chemotherapy.
   - Refractory to Rx.
   - Palliate and stabilise with maintaining QOL.

Therapeutic window :

- Chemotherapeutic agents have a narrow therapeutic window.
- The effectiveness starts from the minimum effective dose upto the minimum toxic dose.
- Therapeutic index = median lethal dose - median effective dose.



Combination chemoherapy :

- more effective in attacking heterogenous population
- Different MOA decreases drug resistance
- Has a synergistic effect.
- Optimal dose & schedule to be used.
- There will be different toxicities which are at manageable level.
- Sequencing with other modalities like Sx or RTx.
- more commonly used combination is carboplatin + paclitaxel.

Dosing :

- BSA based : Dosing in mg/m^a
- Dose intensity :
  Increasing the dose without increasing the frequency.
  Risk of toxicity.
- Dose density :
  Increase the frequency and reduce the dose accordingly.
- Routes : Oral/iv/sc/im/ip.

Toxicities

00:39:37

Extravasation :

One of the effect of toxicities is the extravasation injury.

Types of extravasation :

- Vesicants : Agents capable of caiusing skin ulceration and tissue necrsosis on extravasation.
- Exfoliant : Agents capable of causing skin exfoliation on extravasation.
- Irritant : Agents capable of causing skin irritation on extravasation.
- Inflammant : Agents capable of causing skin inflammation on extravasation.

Management :

- Stop infusion → elevate affected arm → Ice packs.
- If severe → Plastic Sx.
- may require analgesics/antiemetics/antibiotics.

Chemotherapeutic agents and their association with extravasation injury

Vesicants	Exfoliants	Irritants	Inflammants	Neutral
Dactinomycin	Cisplatin	Carboplatin	Methotrexate	Bleomycin
Doxorubicin	Docetaxel	Etoposide		Cyclophosphamide
Paclitaxel	Liposomal doxorubicin			Gemcitabine
	Topotecan			Ifosfamide

Vesicant	-	Agent capable of causing skin ulceration and tissue necrosis on extravasation
Exfoliant	-	Agent capable of causing skin exfoliation on extravasation
Irritant	-	Agent capable of causing skin irritation on extravasation
Inflammant	-	Agent capable of causing skin inflammation on extravasation

Hypersensitivity reactions :

One of the common agent causing hypersensitivity is paclitaxel.

Management :

Management of Hypersensitivity Reactions

1. Stop the chemotherapy infusion
2. Assess the patient's airway, breathing, and circulation
3. Administer intravenous normal saline if hypotensive
4. Administer oxygen if dyspneic or hypoxic
5. Administer intravenous antihistamine (e.g., 50 mg intravenous diphenhydramine or 25–50 mg intravenous promethazine)
6. Administer 5 mg of nebulized salbutamol if the patient has bronchospasm
7. Administer intravenous corticosteroids (e.g., 100 mg of hydrocortisone); this may have no effect on the initial reaction, but may prevent rebound or prolonged allergic manifestations
8. If the patient does not promptly improve or has symptoms of persistent or severe hypotension or persistent bronchospasm or laryngeal edema, administer adrenaline or epinephrine (0.1-0.25 mg intravenous); further acute resuscitation measures may be required
9. Reassure the patient that the problem is a recognized and treatable one

Note :

Methotrexate interacts with warfarin. Hence the dose of warfarin must be decreased if given along with methotrexate.

Drug resistance and response 00:45:10

Resistance :

Drug resistance can be :

- Intrinsic.
- Acquired.

Causes :

- Increased drug efflux.
- Inactivation of the drugs.
- Target is inactivated/changed.
- Activation of DNA repair.
- Reversion of mutations.

Response :

Response is based on response evaluation criteria in solid tumors (RECIST) criteria.

Clinical end points in evaluating response to chemotherapy

End Point	Definition
Complete response (CR)	Disappearance of all measurable "target" lesions
Partial response (PR)	A decrease of ≥ 30% in the sum of diameters of all target lesions
Progressive disease (PD)	An increase of ≥ 20% in the sum of diameters of target lesions or the identification of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD

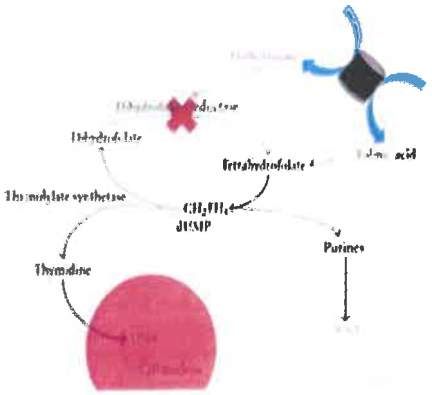
Chemotherapeutic agents 00:52:41

Antimetabolites :

- Analogues of naturally occurring components of metabolic pathways.
- S phase specific.
- Effective in rapidly growing tumor with short doubling time and large GF.

methotrexate :

- Indication : GTN.
- Blocks DHFR
- Route : Oral/im/iv/it.
- 8 day regime.
- Given on days 1, 3, 5, 7. Dose : 50 mg/m^a



methotrexate action.

Leucovorin :

- Given on days 2, 4, 6, 8.
- Dose : 0.1 mg/kg.
- Toxixcity : myelo suppression/renal toxicity/cerebral dysfunction.

Gemcitabine :

- Indications : Recurrent ovariancarcinoma/uterine sarcoma.
- Synthetic nucleoside analogue.
- 30 min infusion. Dose : 1250 mg/m^a once weekly for3 wks with one week off.

Chemotherapy antimetabolites used for gynecologic cancer

Generic name	Brand name	Indications	Routes	Common dosages	Common toxicity
Methotrexate	Trexall, Rheumatrex	GTN	PO, IM/IV, intrathecal	IM: 1 mg/kg on days 1, 3, 5, 7 of 8-day cycle or 30-50 mg/m^2/wk IV: 100 mg/m^2 during 30 min, then 200 mg/m^2 during 12 hr	BMD, mucositis, renal toxicity, CNS dysfunction
Gemcitabine	Gemzar	Recurrent ovarian CA, uterine sarcoma	IV	600-1250 mg/m^2/wk over 30 min x 2-3 wk	BMD, N/V/D, malaise and fever
5-Fluorouracil	Adrucil	Cervical CA, vulvar CA	IV	800-1000 mg/m^2/d during 96 hr	Mucositis, PPE
	Efudex	VAIN	Vaginal cream	3 mL QOD x 1 wk, then weekly up to 10 wk	Vulvovaginal irritation

BMD - Bone marrow depression
CA - Cancer
CNS - Central nervous system
GTN - Gestational trophoblastic neoplasia
IM - Intramuscular
IV - Intravenous
N/V/D - Nausea, vomiting, and diarrhea
PPE - Palmar-plantar erythrodysesthesia
PO - Orally
QOD - Every other day
VAIN - Vaginal intraepithelial neoplasia

Antitumour antibiotics :

Actinomycin D :

- Indication : GTN.
- Single agent or combination (EMACO).
- Pulse dose : 1.25 mg IV push every other week.
- Toxicities : BMD, alopecia, vesicant.

Bleomycin :

- Used in BEP regime for GCT.
- Role in G2 phase, palliative for pleural effusion by pleurodesis.

- Pulmonary toxicity :

  Seen in 10% with 1% death prevalence.

  If DLCO is decreased by 15-30% → Impending pulmonary toxicity →

  Drug must be stopped.

  Dose >400 u is not recommended.

Doxorubicin :

- Indication : Ovarian carcinoma/uterine sarcoma.
- Intercalate with DNA, inhibit topoisonerare II and produces free radicals.
- Dose : 60 m g/m^2 3 weekly.
- Toxicty :

  Cardio toxicity (If cummulative dose >550).

  Pegylated liposomal doxorubicin decreases cardiotoxicity, but increases palmo plantar erythodysesthesia.

  Dose : 40 mg/m^2 every 4 weekly.

Chemotherapeutic antibiotics used for gynecologic cancer

Generic name	Brand name	Indications	Route	Dosages	Toxicity
Actinomycin D (dactinomycin)	Cosmegen	GTN	IV	1.25 mg IV push every other wk or 0.5 mg on days 1-5 every 2-3 wk	BMD, N/V ⊗, alopecia, vesicant
Bleomycin	Blenoxane	Germ cell or SCST ovarian CA, GTN	IV, IM, SC, intrapleural	IV 20 U/m^2 (maximum dose of 30 U) every 3 wk	Pulmonary toxicity, fever, skin reaction
Doxorubicin	Adriamycin	Uterine sarcoma, recurrent epithelial ovarian CA	IV	45-60 mg/m^2 every 3 wk	BMD, cardiac toxicity, alopecia, vesicant
Liposomal doxorubicin	Doxil	Recurrent epithelial ovarian CA	IV	40-60 mg/m^2 over 30 min, every 4 wk	PPE, stomatitis, infusion reaction

Plant alkaloids :

Taxanes :

- Paclitaxel/docetaxel.
- Cell cycle specific.
- Acts on m phase.
- Derived from yew tree.
- Prevent depolymerization of spindle.
- Toxicity : myelosuppression, hypersensitivity reaction, peripheral neuropathy.

Chemotherapeutic plant alkaloids used for gynecologic cancer

Generic name	Brand name	Indications	Routes	Dosages	Toxicity
Paclitaxel	Taxol	Recurrent epithelial ovarian CA, endometrial CA, cervical CA, GTN	IV, IP	IV: 135-175 mg/m^2 every 3 wk, or 80 mg/m^2/wk for 3 weeks IP: 60 mg/m^2 on day 8 following a day-1 IV dose	HSR, peripheral neurotoxicity, BMD, alopecia, bradycardia and arrhythmia
Docetaxel	Taxotere	Recurrent epithelial ovarian CA, uterine sarcoma	IV	75-100 mg/m^2 every 3 weeks, or 35 mg/m^2/week for 3 weeks	BMD, peripheral edema, HSR, alopecia
Vincristine	Oncovin	GTN	IV	0.8-1.0 mg/m^2 every other week	Neurotoxicity, abdominal pain, alopecia
Etoposide	VP-16	Germ cell or SCST ovarian CA; recurrent epithelial ovarian CA	IV, PO	IV: 100 mg/m^2 days 1 & 2, every 2 wk, or 75-100 mg/m^2, days 1-5, every 3 wk PO: 50 mg/m^2/day for 3 wk	BMD, alopecia, secondary cancers
Topotecan	Hycamtin	Recurrent epithelial ovarian CA, cervical CA	IV	1.5 mg/m^2/d, days 1-5, every 3 wk, or 4 mg/m^2/wk for 3 wk, or 0.75 mg/m^2/d, days 1-3, every 3 wk	BMD, N/V, alopecia, fever, malaise

Platinum compunds :

Carboplatin :

- Produce DNA adducts and inhibit DNA synthesis.
- Toxicty : myelosuppression (Thrombocytopenia).
- Dose calculation : Based on area of the curve (AUC)which is based on GFR.
- Calvert formula : Carboplatin total dose (mg) = AUC × (GFR + 25). GFR = Creatine clearance.
- Cockcroft-Gault equation : Cr. clearance = (140 − age) × wt/0.72 × S. Cr.

Cisplatin :

- Toxicity : Nephrotoxicty, neurotoxicity and ototoxicity. myelosuppression is less common.

PRINCIPLES OF RADIOTHERAPY : I

Introduction

00:00:32

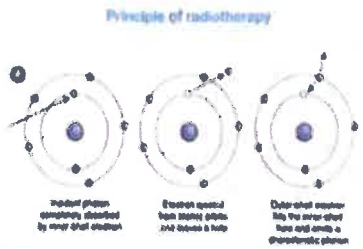
Features :

- Radiation therapy is a critical component in the multidisciplinary management of majority of adult female cancers.
- Primary therapeutic modality in advanced cervix, vulvar, and vaginal cancers (As m/c histology is squamous cell CA/SCC).
- Adenocarcinomas originating uterine cancers : Radiation is often indicated as adjuvant therapy, post-resection.

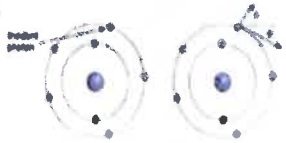
Role of radiotherapy :

Intent.	Site.
Curative.	Cervix, vulva, vagina, uterus.
Adjunctive to surgery.	Cervix, vulva, vagina, uterus.
Palliative.	Metastasis causing symptoms : Bleeding, pain, obstruction.

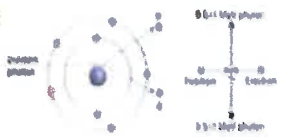
Principle of radiotherapy :



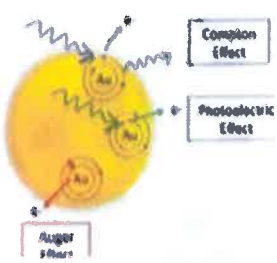
- Ionising radiation is used.
- Atom is converted into ion.
- Both direct and indirect DNA damage.
- Incident photon energises the inner shell electron → Energised electron moves out → Void of electron → Electron from the outer shell comes to inner shell → An amount of energy is released in the form of photon.



- Compton effect : Incident photon does not give the entire energy → Electron itself gets displaced and another photon is separated.



- Pair production : Incident photon will cause the release of an electron and positron → Releases a large amount of energy in the form of photon.



Types of radiotherapy :

Radiation treatments can be performed in two different ways :

1. External beam radiation therapy (EBRT)/teletherapy : Radiation source is at a distance from the target organ.
2. Brachytherapy :
    - Interstitial brachytherapy : Radiation source is kept directly into the tumour.
    - Intracavitary brachytherapy : Radiation source is kept into the body cavity close to the tumour.

EBRT

00:09:38

Types of EBRT :

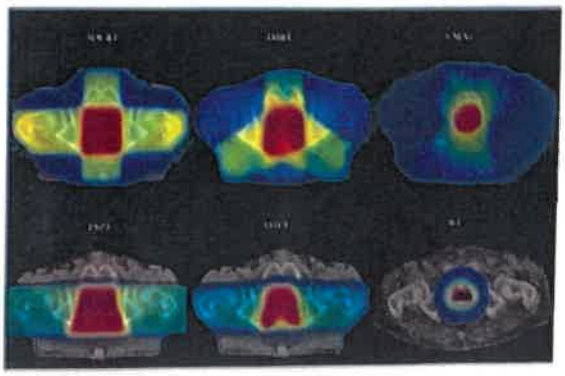
Conventional :

- Lateral view field and AP-PA view field is present.
- Maximise the ionising radiation to the tumour.
- Uses single or opposing beams, with or without 2D dose distributions, with compensators and simple shielding for organs at risk (OAR).
- Less conformity.

3DCRT (3D Conformal Radiotherapy) :

- 3D images like CT and MRI images are used.
- Target volume delineation of tumour and normal organs according to ICRU principles with 3D dose calculations using MLC to shape beams.
- Multi-leaf collimators.

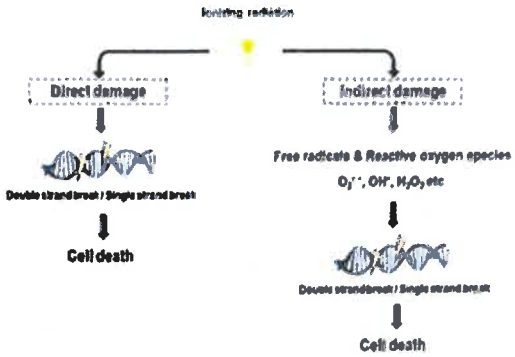
IMRT/IGRT :



- Intensity modulated radiotherapy.
- Intensity of very single beam can be modulated.
- Collimators and subcollimators can be used to modulate the radiation beams.
- Aims : Get as closer/conformal to the shape of the tumour and reduce toxicity to the nearby organs.
- To shape the fluence of the beam.
- Dynamic treatments : Image guided radiotherapy (IGRT).

5 R's of radiobiology :

i. Repair.
ii. Repopulation.
iii. Reassortment.
iv. Reoxygenation.
v. Radiosensitivity.



Effect of ionizing radiation.

Repair :

- Dose of 90 Gy is required to kill the tumour.
- But a single dose can affect the nearby tissues : To avoid this fractions / fractionation of the dose is done.
- Repairing time required for tumour cells will be more as the repair mechanism would be damaged in the tumour cells when compared to normal cells.

Repopulation :

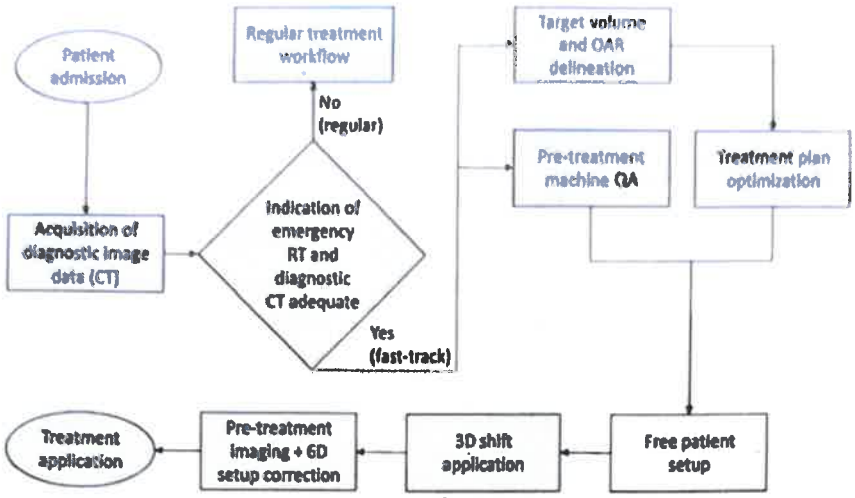
- Late S phase is the most radioresistant phase.
- M phase is the most radiosensitive phase.
- When the radiation is given to the tumour cell, not all the cells will be in G2M phase → Cells in G2M phase will get killed while the other cells are not killed → These cells will try to repopulate → To avoid this fractionation/fractions of doses are given.

Reassortment : Dose should be calculated based on normal cells and tumour cells in the tumour.

Reoxygenation :

- Oxygen is a very good radiosensitizer.
- Radiosensitizer : An element that is added with radiotherapy which has a synergistic effect.
- In well oxygenated tissue, radiotherapy is rapid as it releases more free radicals.
- While in less vascular/oxygenated tissue the radiotherapy is very slow → In anemia radiotherapy is difficult.

Note : When chemotherapy is given along with radiotherapy the dose of chemotherapy is reduced as radiotherapy has radiosensitising property.

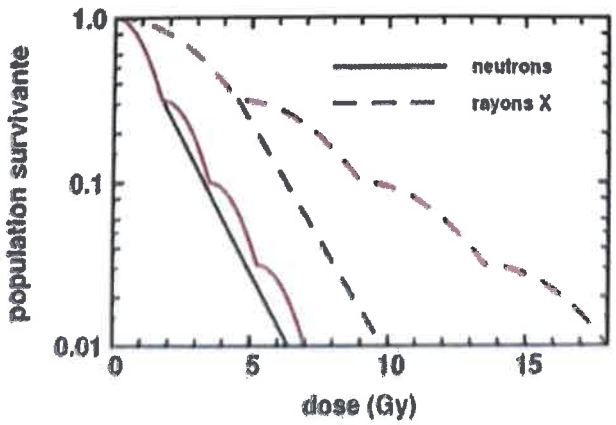


Algorithm for EBRT.

Standard fractionation :

00:39:03

- Successful eradication of a localized cancer requires that the cancer cells be killed more rapidly and efficiently than surviving cancer cells can proliferate and repopulate.
- Delivery of this dose over the shortest feasible elapsed time will maximize efficacy along with deleterious consequences of a high dose per fraction on normal tissues.
- This can result in delayed radiation injury expressed months or years after therapy completion.
- Radiation delivered with curative intent is generally administered in daily treatments (Monday through Friday) of 1.8 Gy to 2.0 Gy.
- Cumulative doses range from 45 -70 Gy.
- Risk of delayed injury is lessened when short courses of radiation are administered with palliative intent, often in dose fractions of 2.5 Gy to 4.0 Gy.



Dose response curve.

From the above graph fractionation helps in preventing toxicity to normal cells.

Hyperfractionation :

Increase the number of doses in a day but with constant total dose.

Accelerated hyperfractionation :

Increase the number of doses but decrease the total time.

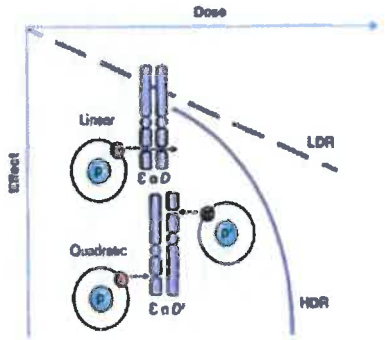
Hypofractionation :

Increase in the dose but decrease in the total treatment time.

α/β ratio :

- As we increase the dose : Initially the effect is proportional to dose but later when the dose increased the effect becomes proportional to square of dose.
- This is called linear effect and quadratic equation.
- α is the linear effect while β is the quadratic effect.
- If the α/β ratio is higher (10) : Killing power is more.
- α/β ratio is lower in normal cells (3).
- Alpha/beta ratio → Response of normal tissues to radiation.

Dose-response curve for HDR irradiation



Cell killing by radiation is largely due to aberrations caused by breaks in two chromosomes. The dose response curve for HDR irradiation is linear quadratic: the two breaks may be caused by the same electron (dominant at low doses) or by two different electrons (dominant at higher doses). For LDR irradiation, where radiation is delivered over a protracted period, the principal mechanism of cell killing is by the single electron.

Early-responding tissues have a high alpha/beta ratio :

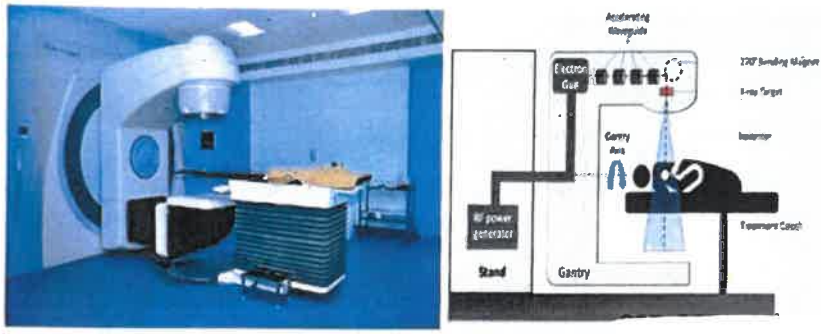
- manifest early reactions to radiation.
- Tissues with high proliferation rates such as bone marrow, reproductive organs and gastrointestinal tract mucosa.
- Preventatively, by administering multiple small radiation dose fractions, there is more sublethal damage repair, and early acute reactions can be decreased.

Late-responding tissues have low alpha/beta ratio :

- Clinical reactions only weeks-months after completion of radiotherapy.
- Slow to respond.
- Lung, kidney, spinal cord and brain are affected.
- More time is needed to repair sublethal damage, and thus high-dose per raction radiation therapy.

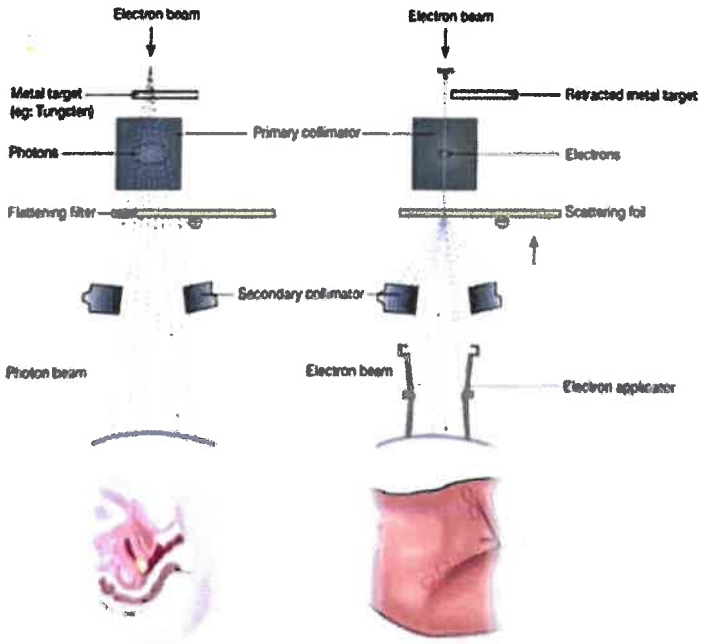
LINAC :

- Linear accelerator.
- High speed electron beam activated by electric field.
- Electrons are channelised to a heavy metal (Tungsten) : x rays (Photons) are released.
- Direct electron beam can be directed at a scattering foil : Electron beam becomes main source of radiation (Electron beam therapy) for superficial structures.



LINAC radiology machine.

Block diagram of a linear accelerator used to create external beam radiation



Differences between types of radiotherapy

A.Conventional radiotherapy | B.Conformal radiotherapy (CFRT) without intensity modulation | C.CFRT with intensity modulation (IMRT)

Steps :

- Initial consultation.
- Simulation (Imaging, immobilisation, tattooing).
- Treatment planning (Target volume delineation, contouring, dosing).
- Treatment delivery.
- Post-treatment follow up.

Planning technique :

- Positioning & Immobilization.
- Simulation.
- Field design.
- Beam energy.
- Dose & fractionation.

Positioning & Immobilization :

Patients may be positioned in :

- Supine position.
- Prone position with belly board.

Supine position is preferred because :

- most comfortable.
- Reproducible position.
- Stabilizes pelvis.
- Can be combined with immobilization devices.

Simulation :

- CT-based simulation is the m/c technique for gynecologic malignancies, treatment planning for both external beam radiotherapy (EBRT) and brachytherapy applications.
- Patient position : Supine with arms on the chest, knee and lower leg immobilisation to prevent pelvic rotation.
- Inferior border of tumour is marked with radio-opaque material.
- Bladder protocol is used to maintain a constant bladder filling 'comfortably full'.
- Orthogonal laser beams are aligned with anterior and lateral tattoos marked with radio-opaque material.
- AP and lateral simulator films are taken.
- Standard field borders are decided using bony anatomical landmarks (x ray sim).

Field borders (AP-PA fields) :

Superior border :

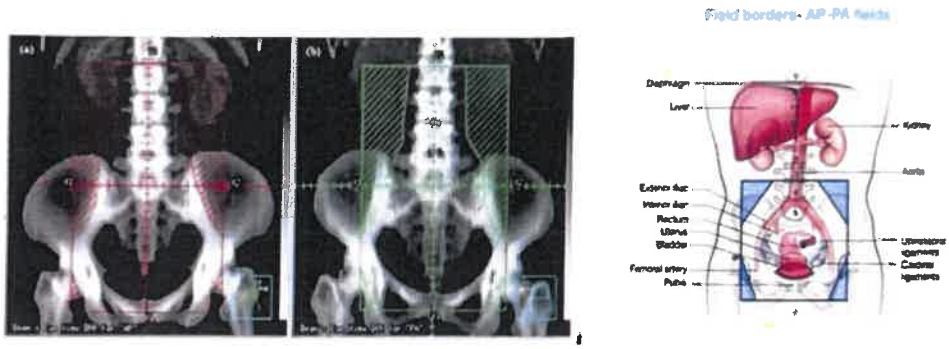
- At the L4-S1 space to include external & internal iliac LN.
- Extended to the L3-4 space if common iliac nodal coverage is indicated.
- Extended to the T11-12 space if paraaortic coverage is indicated.

Inferior border :

- At inferior border of the obturator foramen.
- For vaginal involvement : 3 cm below the lower most extent of disease.

Lateral borders :

- 1.5 – 2 cm margin on the widest portion of pelvic brim.
- Tumours that involve lower third of vagina, inguinal nodes should be included in the fields.



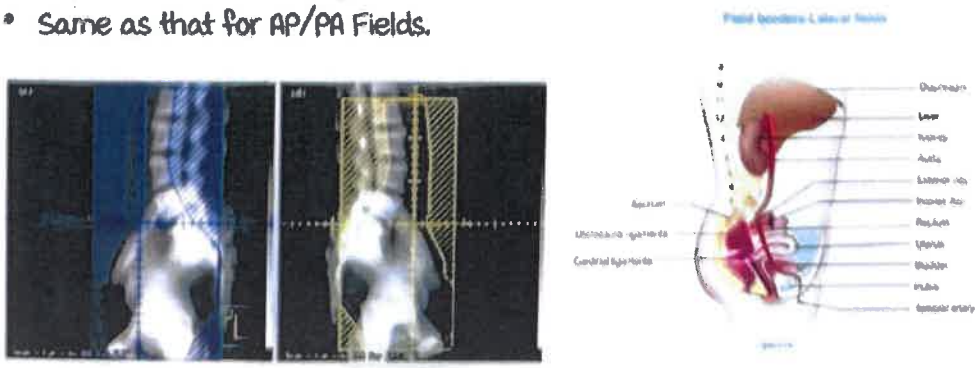
Field borders.

Field borders (Lateral field) :

Anterior margin : vertical line to the anterior edge of pubic symphysis to cover external iliac lymph nodes.

Posterior margin :

- At S2 – S3 junction.
- Extend to sacral hollow in patients with advanced tumours to cover uterosacral ligaments, cardinal ligaments & presacral lymph nodes.
- Superior & inferior margins.
- Same as that for AP/PA Fields.

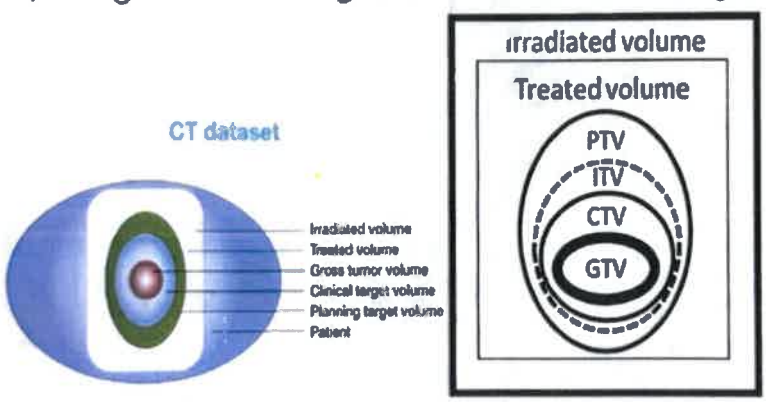


Field borders : Lateral field.

- AP-PA treatments to the para-aortic nodal chain may overdose the kidneys, spinal cord, and small bowel.
- Spinal cord dose (T12 to L2/3) should be kept to <45 Gy & kidney dose to <18 Gy.
- 4 field> 2 field.

CT scanning :

- Superior and inferior limits noted.
- Orally or intravenously administered contrast for tumor localization.
- Reference marks placed on the patient.
- Transfer of the CT dataset to the treatment planning station : Orientation of the patient/treatment coordinate system without the presence of the patient.
- Secondary imaging datasets such as diagnostic CT, MRI, PET can be fused with the primary CT dataset for greater localization of the target volume.



- GTV : Gross disease seen clinically or in imaging studies.
- CTV : Clinically suspected extension of the tumor beyond the gross disease.
- ITV : margin to account for the internal movement of CTV.
- PTV : margin needed to compensate for any setup error.
- Critical structures, organ at risk (OAR) volume has also been defined by the ICRU.

3DCRT

01:03:33

Features :

- Radiation field is tightly conformed 3D shape of PTV by therapeutic dose-volume while minimizing surrounding normal tissue dose as low as possible.
- Treatment session is of 3DCRT comparatively similar to conventional technique around 10-20 min, except the first day of the session.