Gulf Federation For Cancer Control (GFFCC)

GULF FEDERATION FOR CANCER CONTROL (GFFCC)

GUIDELINES

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Part-1

بسم الله الرحمن الرحيم

INTRODUCTION

Dear Colleagues and friends,

It is an honor to give the introduction on this unique effort to produce the first guideline which took 3 years to prepare with the help of consultant oncologists, specialists and most of them are from Kuwait Cancer Control Center (KCCC).

We are taking similar formula which is made by King Faisal Specialist Hospital and Research Center (KFSHRC) to unite the guidelines in gulf region.

I would like to thank consultants who work with me hard to prepare this guideline and also consultants from Gulf area for their review,

This guideline is adapted by radiation oncology department (KCCC) to be their guidelines, this give credit for our guideline.

Dear colleagues and friends, as you know this guideline is first attempt in GCC and we will be more happy to receive feedbacks/comments/suggestions on this guideline in order to improve our work and review and update every year.

Despite importance of guideline, we should know that personalized medicine is taking the priority in patient management with multidisciplinary team decision, and we should not forget that every clinical decision needs to match general concept in guideline with patient criteria and needs. This will be the best treatment option for the cancer patients.

Again I would like to thank my colleagues in spending a lot of time and effort to help in completing this guideline.

I am waiting to hear from you soon.

Thank you very much

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Chairman | Radiation Oncology Department | Kuwait Cancer Control Center (KCCC)

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GROUP (A)

1. Brain tumors.
2. Genitourinary malignancies.
3. Gynaecological malignancies.
4. Soft tissues sarcoma.
5. Hodgkin's and non-Hodgkin's Lymphoma.

A.1- BRAIN TUMORS CLINICAL MANAGEMENT GUIDLINES

1. Epidemiology

The incidence of primary malignant brain tumours has been increasing especially in elderly person (rates are increasing at about 1.2% each year). These tumours show marked heterogeneity, so the prognostic features and treatment options must be carefully reviewed for each patient. The ASIR for Kuwaiti male & female is 3.1 & 2.3 as compared to 1.2 & 1.8 for Non-Kuwaiti respectively, which is 2.5 & 1.6 for GCC & 3.9 & 3.0 for the World.

2. Clinical Presentation

Patients with brain tumors often present with any of the following:

2.1 Symptoms of increased intracranial pressure (Headache, Vomiting, blurred vision)
2.2 Seizures,
2.3 Focal neurologic findings related to the size and location of the tumor and to the associated peri-tumoral oedema.
2.4 Obstructive hydrocephalus in Ependymoma.
2.5 Visual symptoms in craniopharyngioma.

3. Diagnostic Work up

3.1 History & Physical examination
3.2 CBC, Biochemistry profile
3.3 Review of pre & post-op MRI images

- A post-operative MRI with and without contrast should be obtained 24-72 hours after surgery to document the extent of disease after surgical intervention.
- MRI of Brain & Spine should be done in Ependymoma and Medulloblastoma.

3.4 Review of histopathology at referral center.

After initial work up patient is planned for local radiotherapy ± chemotherapy as per protocol depending on histopathology as mentioned below.

4. Staging:

No specific TNM staging for Brain tumors

5. Prognostic factors:

5.1 Histology
5.2 Age
5.3 Performance status
5.4 Duration of symptoms
5.5 Extent of surgical excision.

6. Treatment

The involvement of interdisciplinary team including neurosurgeon, radiation oncologist, neurologist, neuro-radiologist, is a key factor in the appropriate management of these patients.

6.1 Surgery :

Neurosurgeons generally provide the best outcome for these patients if they remove as much lesion as possible, keep surgical morbidity to a minimum and ensure an accurate diagnosis. Surgical options include stereotactic biopsy, open biopsy or debulking procedure, subtotal resection or gross total tumor resection where feasible. The pathologic diagnosis is critical and often difficult to determine accidentally. Therefore as much tissue as possible should be delivered to the pathologist, review by an experienced neuro-pathologist is highly recommended. Patients are referred from neurosurgical unit mainly from Ibn Sina hospital after Craniotomy & maximal safe debulking and after discussion in a multidisciplinary meeting.

6.2 Management according to Histopathological type

6.2.1 Low Grade Glioma:

(Astrocytomas, Oligodendrogliomas, Oligoastrocytomas – Grade 1 & II)

It is divided into Low Risk and High Risk, Low Grade Glioma.

6.2.1.1 Low Risk criteria:

- Age ≤ 40 yrs.
- KPS ≥ 70.
- Minor or no Neurologic deficit.
- Oligodendroglioma or Mixed Oligoastrocytoma.
- Tumor dimension< 6 cm.
- 1p and 19q co-deleted and IDH1 or 2 mutated.

6.2.1.2 High Risk (if three or more of following):

- Age ≥ 40 yrs.
- KPS under 70.
- Tumor dimension> 6 cm.
- Tumor crossing midline.
- Pre-op Neurological deficit of more than minor degree.
- Astrocytoma.

6.2.1.3 Other adverse factors include:

- Increased perfusion on imaging.
- One or no deletion of 1p &19q.
- Wild type IDH 1 or 2.
- If gross total resection is achieved, most low risk patient may be observed without adjuvant therapy with close follow up.

- High Risk patients will take adjuvant Radiotherapy or Chemotherapy (if 1p 19q co-deleted).
- Patient who had a stereotactic biopsy, open biopsy or sub-total excision should be treated with immediate post-op Radiotherapy or Chemotherapy.

6.2.1.4 Treatment: Maximal safe resection is recommended.

6.2.2 High Grade Glioma:

- More than 50% of all gliomas.
- Age: 45 – 55 yrs.
- Grade III (Anaplastic astrocytoma).
- Grade IV (Glioblastoma multiforme)
- CT / MRI findings: diffuse infiltration, cross midline, mass effect and oedema enhances with contrast.

6.2.2.1 Treatment: Surgery in the form of maximal safe excision followed by Radiotherapy + Concomitant & Adjuvant Temozolomide.

6.2.3 Oligodendroglioma:

- <15% of all primary brain tumor.
- 5-% in frontal lobe.
- Radiologically well demarcated, do not enhance with contrast, calcification present.

6.2.3.1 Treatment:

Young patient with complete resection: only follow up.
If incomplete resection: low and intermediate grade – post.op Radiotherapy.
Anaplastic: Radiotherapy + Concomitant Temozolomide.

6.2.4 Ependymoma:

- Arising from Ependymal cell lining of the ventricular system and central spinal canal.
- 60 – 70% is post fossa within 4th ventricle.
- Children 2/3 supratentorial and 1/3 infra-tentorial, adults reverse.

6.2.4.1 Treatment: Primary surgery – maximal safe debulking, Radiotherapy - incomplete resection/recurrence

6.2.5 Medulloblastoma:

- Medulloblastoma mainly presents in children in the roof of the fourth ventricle.
- Initial treatment is surgical debulking followed by craniospinal radiotherapy in children over 3 years. The dose of which will depend on the risk factors to be discussed below.
- Children below 3 years are treated with chemotherapy alone.

6.2.5.1 Treatment: Patient undergoes maximum debulking surgery and further treatment depends on the amount of residual disease left behind and other risk factors.
The patient is divided into:

6.2.5.1.1 Standard Risk Medulloblastoma

Histologically proven medulloblastoma, including the following variants (WHO classification)

- classic medulloblastoma
- nodular / desmoplastic medulloblastoma
- melanotic medulloblastoma
- medullomyoblastoma
- Pathology review should be undertaken if any doubt as to the variant of medulloblastoma
- No CNS metastasis on MRI – (supratentorial, arachnoid of the posterior fossa or spine) It is recommended that MRI scan of the head and spine be performed before surgery.
- If spinal axis imaging has not been performed before surgery, it should be performed before lumbar puncture in order to avoid artefacts (if positive in such circumstances, spine MRI should be repeated).
- No clinical evidence of extra-CNS metastasis.
- No tumour cells on the cytology of lumbar CSF.
  Lumbar puncture should generally be performed at least 15 days following surgery. If a lumbar puncture is performed before 15 days and is negative for tumour cells then this will be taken as evidence of non-metastatic disease. If, however, the CSF is positive by lumbar puncture before 15 days then the lumbar puncture must be repeated at 15 days or beyond to determine M1 status.
- Patients with residual disease $\leq$ 1.5 cm^2 - following initial or second look surgery.

6.2.5.1.2 High Risk Medulloblastoma according to risk factors

Not to be treated with 23.4 Gy Craniospinal Radiotherapy

- Large cell medulloblastoma
- Metastatic medulloblastoma (on CNS MRI and/or positive cytology of postoperative lumbar CSF).
- Patients with residual disease > 1.5 cm^2 - following initial or second look surgery.

6.2.5.2 Summary of Treatment

6.2.5.2.1 Standard Risk Treatment Protocol

Surgery ⟶ **Standard RT 23.4/54 Gy +Vincristine** ⟶ **Chemotherapy** CCNU, Cisplatin, Vincristine **8 Cycles**

Chemotherapy 8 Cycles given at 6 weekly intervals

V – Vincristine 1.5 mg/m^2 (maximum 2 mg)

C – Lomustine (CCNU) 75 mg/m^2

P - Cisplatin 70 mg/m^2

Weeks					
1	2	3	4	5	6
V------	V------	V------	------	------	------
C					
P					

- MR of head and spine (preferably before surgery) must be performed.
- Post op MR without/with contrast within 72 hr (preferably 24-48 hrs).
- Inform department of radiation oncology as soon as possible after diagnosis to avoid any delay in starting radiotherapy.
- LP from day 15 after surgery.
- RT should start within 40 days of surgery (preferably within 28 days).
- First course of maintenance chemotherapy starts 6 weeks after RT.

6.2.5.2.2 High Risk Treatment Protocol

Patients to be treated with 36 Gy craniospinal irradiation with a total of 54Gy to the posterior fossa. Ther aspects of treatment will be the same as in the guidelines for standard risk Medulloblastoma.

Residual tumour > 1.5 cm^2 after first or second surgery.

In situations where the post surgical residuum exceeds 1.5 cm^2, second surgery is recommended to remove the residual disease as far as possible.

In cases where after first or second surgery the residual is greater than 1.5cm^2 then the general recommendation is for patients to receive 36 Gy craniospinal with a total of 54Gy to the posterior fossa as for patients with Large Cell Medulloblastoma, with other aspects of treatment the same as in the guidelines for Standard Risk Medulloblastoma.

However, on an individual basis in young children with a significant residuum after first or second surgery, it may be felt that the neuropsychological sequelae of 36 Gy craniospinal radiotherapy outweigh the possible increased risk of relapse in using a dose lower than this. In such cases where doubt exists, such cases should be discussed individually.

6.2.5.3 Timing of Radiotherapy

Following definitive surgery - all patients should begin RT within 40 days but preferably within 28 days.

6.2.6 Brain metastases:

- 10 times more frequent than primary brain tumors (PBT).
- 20 – 40% cases with cancer.
- Most common with lung, breast, unknown primary and melanoma.
- 80% cerebrum, 15% cerebellum, 5% brain stem, 70 are multiple.

6.2.6.1 Treatment:

- Medical decompression with Decadron / Mannitol.
- Surgery for 1- 2 lesions followed by whole brain Radiotherapy.
- Radiosurgery for limited number (typically 1-4) brain metastases with or without Whole Brain Radiotherapy (WBRT) or salvage treatment following prior WBRT.
- Multiple lesions – Whole Brain Radiotherapy.

6.2.7 Craniopharyngioma:

- Benign tumor: 8 – 14 yrs.
- Arise from squamous cell nest in region of pituitary stalk.
- CT / MRI: cystic lesion in region of pituitary stalk.

6.2.7.1 Treatment:

- Surgery. If complete excision - for follow up.
- Radiotherapy: Incomplete excision / recurrence:

6.2.8 Meningioma:

6.2.8.1 Surgery: Neurosurgeon to consider for complete excision

6.2.8.2 Indications of Radiotherapy

- **Histology :** Grade II (partial excision) / Grade III
- Infiltration of adjuvant brain
- Recurrence.
- If in-operable, as primary treatment.

6.2.8.3 Post operative: Pre-surgical MRI is fused with planning CT scan and areas of greatest risk of recurrence are defined as the points of attachment to the dura, any meningeal extension, intravascular, bony involvement or invasion into the brain.

6.2.9 Pituitary Gland:

6.2.9.1 Surgery – trans sphenoidal approach, big tumors may need Craniotomy

6.2.9.2 Indications of Radiotherapy

- For patients who have residual lesion after surgery.
- Recurrence following surgery.
- Rarely in in-operable cases, as primary modality.

7. Radiotherapy Protocol

If patient is a candidate for post-operative Radiotherapy:

- Head cast & back cast if spinal irradiation is indicated for immobilization.
- CT simulator for scanning area and Geometrical reference point.
- Planning CT scan 0.5 cm. slices with contrast.
- Transfer of data to Planning system.
- Marking GTV, CTV as per different histology of Brain tumors as mentioned below and final PTV along with critical organs& approved by consultant Radiation Oncologist.
- Planning by physicist and approval of best plan by consultant. (Dose as per tumor histology).
- Plan evaluation on Simulator with verification by Radiation Oncologist.
- Final evaluation on treatment machine with verification of plan to first set up by Radiation Oncologist during treatment.

7.1 External Beam: Planning Technique

7.1.1 Patient preparation

- Patient is preferably asked to come nil orally with RFT on previous day as contrast has to be administered

7.1.2 Immobilization

- Preparation of cast (orfit).
- It is done in supine position and if the lesion is close to the eyes, flexion of the neck is considered so that Reid's line is perpendicular to the table which will help in positioning of the beam away from the eyes.
- For craniospinal Radiotherapy for Medulloblastoma & indicated cases of
- Ependymoma prone position is considered & head & upper back cast is made.

7.1.3 Orientation, set-up, marking and reference points

- On CT simulator, geometrical reference mark is fixed and area to be scanned is marked along with anterior and lateral lasers for reproducing position. CT scan position is verified with anterior and lateral lasers marked on cast.

7.1.4 Image acquisition

- CT cuts done with slice thickness 0.3 – 0.5 cm with contrast, early and delayed images are required to visualize the tumour properly. These data is transferred to ARIA / CMS.

7.1.5 Target definition:

7.1.5.1 GTV:

- Gross tumor is marked (by the help of MRI fusion of T2 flair/ T1 contrast images to contrast enhanced planning CT images for accurate delineation of the tumor on ARIA or CMS).
- For Pituitary tumors, GTV: any abnormality showing contrast enhancement on T1W MRI

7.1.5.2 CTV:

7.1.5.2.1 Low Grade Glioma

- CTV: GTV + 1.5 cm. margin with adequate modifications (to cover sub-clinical disease and exclude OAR).

7.1.5.2.2 High Grade Glioma

- CTV: GTV + 2.5 cm. margin with adequate modifications
- CTV Boost: GTV+1.5 cm with adequate modifications
- PTV: CTV + 0.5 cm. margin.

7.1.5.2.3 Oligodendroglioma

- CTV: GTV + 1.5-2cm margin with adequate modifications
- PTV: CTV + 0.5 cm. margin.

7.1.5.2.4 Ependymoma

Craniospinal radiotherapy is given if positive CSF or spinal imaging is positive.

- CTV: GTV + 1 - 1.5 margin with adequate modifications
- PTV: CTV + 0.5 cm. margin

7.1.5.2.5 Medulloblastoma

- CTV: Whole Brain & Spine
- CTV Boost : Posterior fossa
- PTV: CTV + 0.5 cm. margin.

7.1.5.2.6 Brain Metastases

- CTV: Whole Brain
- PTV: CTV + 0.5 cm. margin

7.1.5.2.7 Craniopharyngioma

- GTV: Cystic & solid component (pre & post-op MRI)
- CTV: GTV+ 3-5mm margin
- PTV: CTV + 0.5 cm. margin

7.1.5.2.8 Meningioma

- CTV: GTV+ 5mm margin
- PTV: CTV + 0.5 cm. margin

7.1.5.2.9 Pituitary gland

- NO GTV to CTV margin

7.1.5.3 PTV:

For all tumors, the PTV: CTV + 0.5 cm. margin (for set up and organ motion).

7.1.6 Technique:

Three Dimentional Conformal radiotherapy.

7.1.7 Beam Arrangement.

7.1.7.1 for the brain: Multiple fields plan is acquired and the best plan i.e. plan which provides maximum conformity and minimum dose to critical organ is selected and approved by consultant.

7.1.7.2 Craniospinal fields:

- Lateral opposed fields to cover all intracranial contents and cervical cord.
- Gantry rotation of the lateral brain/cervical cord fields should be matched to the superior border of the spinal field.
- Direct posterior field to cover the whole spine down to the S2–S3 junction in order to treat the entire thecal sac with a margin.
- Extended source-to-skin distance (SSD) or a junctioned third field at the inferior border of the primary spinal field may be necessary.
- Moving junction technique used

7.1.8 Beam Energy

6 – 10 Mv as per plan

7.1.9 Dose prescription & Fractionation

7.1.9.1 Adjuvant Radiotherapy

7.1.9.1.1 – Low Grade Glioma

- 50 – 54 Gy. in 25 – 27 fractions over 5 – 6 weeks

7.1.9.1.2 – High Grade Glioma

- 50 Gy initially, re-evaluation and 10 Gy more with reduced fields if feasible. (Total 60 Gy/30 fractions over 6 weeks)

7.1.9.1.3 - Oligodendroglioma

- 54- 56 Gy in 27-28 fractions over $5_{1/2}$ – 6 weeks.

7.1.9.1.4 - Ependymoma

- If Brain: 54 Gy./30 Fr. ; If Spine: 50.4 Gy./28 fractions.
- Craniospinal Dose : 36 Gy./20 fractions. Primary tumor: boost to primary as above.

7.1.9.1.5 - Medulloblastoma

- **Standard Risk**

Brain – 23.40 Gy in 13 daily fractions of 1.80 Gy.

Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy.
Primary tumour boost – 30.6 Gy in 17 daily fractions of 1.80 Gy.
Total dose to primary – 54 Gy in 30 daily fractions of 1.80 Gy.

- **High Risk RT Regimen**

Brain – 36 Gy in 20 daily fractions of 1.80 Gy.
Spine - 36 Gy in 20 daily fractions of 1.80 Gy.
Primary tumour boost – 18 Gy in 10 daily fractions of 1.80 Gy.
Total dose to the primary – 54 Gy in 30 daily fractions of 1.80 Gy.

7.1.9.1.6 – Craniopharyngioma

- 50 – 54 Gy. in 28 – 30 fractions over 5-6 weeks.

7.1.9.1.8 – Meningioma

- WHO Gr II – 54 – 60Gy in 1.8 – 2Gy/ fr
- WHO Gr III – 59.4 – 60Gy in 1.8 – 2Gy/ fr

7.1.9.1.9 – Pituitary gland

- For small pituitary adenoma: 45 Gy / 25 fractions.
- For large pituitary adenoma: 50.4 Gy / 28 fractions.

7.1.9.2 Palliative Radiotherapy

Brain Metastases

- 30 Gy./10 fractions over 2 weeks
- 20 Gy/5 fractions over 1 week.

7.1.10 Dose limitation to OAR

- Eyes, Lens, Optic nerves, Optic chiasma, Brain stem

As per QUANTEC guidelines

7.1.11 Plan verification and execution:

7.1.11.1 The treatment isocenter on a DRR from the CT simulation is compared with portal images of the isocenter on the treatment machines using electronic portal imaging.
7.1.11.2 Off-line correction protocols are used for standard conformal treatment.
7.1.11.3 Images are taken on days 1 and weekly thereafter with a correction made if the mean error in any one plane is ± 3mm.

7.2 Brachy Therapy

Not applicable

7.3 Sequelae of treatment

7.3.1 Acute:

7.3.1.1 Nausea, Vomiting, Headache, local alopecia.

7.3.2 Sub acute/Early delayed:

7.3.2.1 Occurs 6 – 12 wks after Radiotherapy.
7.3.2.2 Changes in capillary permeability & transient demyelination.
7.3.2.3 Headache, Vomiting.
7.3.2.4 Responds to Steroids.

7.3.3 Late:

7.3.3.1 Radiation Necrosis:

7.3.3.1.1 Occurs 16 months to many years, peaks at 3 yrs.
7.3.3.1.2 Symptoms same, Mimic tumor recurrence on CT Scan.
7.3.3.1.3 PET Scan & MR Spectroscopy are helpful

7.3.3.2 Decrease Visual Acuity: Optic nerve & Optic chiasma if receives 54-60 Gy

7.3.3.3 Hormone Insufficiency: Irradiation of hypothalamic pituitary axis with dose as low as of 20 Gy.

7.3.3.4 Reduction in new learning ability, recent memory & problem solving.

8. Principle of Hormonal Treatment:

Not Applicable

9. Principle of Chemotherapy:

9.1 High grade Glioma

9.1.1 For concomitant: Temozolomide 75 mg/m2 - concomitant daily with EBRT.

9.1.2 For adjuvant and Recurrence: 150- 200mg/m^2 5/28 schedule every 4 weeks adjuvant x 6 courses.

9.2 Medulloblastoma

9.2.1 All patients receive chemotherapy during irradiation.
9.2.2 A total of 8 doses of vincristine will be administered.
9.2.3 The first dose will be given during the first week of RT.
9.2.5 Treatment with weekly vincristine will thus usually extend beyond the end of radiotherapy.
9.2.6 Weekly administration of vincristine will be suspended for breaks in radiotherapy due to myelosuppression or other reason and will recommence when radiotherapy is restarted. In this case, eight doses of vincristine will be given unless toxicity due to vincristine necessitates omission of this drug.
Vincristine 1.5 mg/m^2 (maximum dose 2 mg).
9.2.7 Maintenance Chemotherapy with 8 cycles of CCNU, Cisplatin & VCR every 6 weeks after 6 weeks of Radiotherapy.

10. Management of Recurrence/Relapse

10.1 Surgery if feasible.
10.2 High grade Gliomas: Chemotherapy with dose dense Temozolomide ±

Bevacizumab/CCNU/Irinotecan.

10.3 Oligodendroglioma**:** Chemotherapy with Temozolomide, if failed PCV.

11. Follow Up

11.1 weekly during radiotherapy with blood tests for assessment of treatment related toxicities.

11.2 Every three months with MRI for 1-2 years than 6 – 12 months for another 5 years, less frequent imaging is required beyond 5 years as per histopathology.

12. Ongoing Departmental studies

12.1 Three-Dimentional conformal radiotherapy plus concurrent and adjuvant temozolomide in glioblastoma multiformis. Referral center experiences.

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A.2- PROSTATE CANCER CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

More than 1.1 milion cases of prostate cancer were recorded in 2012, accounting for around 8% of all new cancer cases and 15% in men with an estimated 307,500 deaths in 2012. In US, the estimated new cases in 2016 is 189,00 which represents 21% of all new cases in men. In GCC ASIR is 5.8 (from 2003-2007). In Kuwait, prostate cancer considered 2nd most common cancer among Kuwaiti with age standaridized incidence rate (ASIR) 17.8/ 100.000 while it is the 4th common cancer among non Kuwaiti with ASIR is 11.2.

2. Clinical Presentation:

2.1 Most men presenting with prostate cancer are asymptomatic and diagnosed only because of an elevated PSA or an abnormal digital rectal examination.

2.2 Occasionally a diagnosis is made following a transurethral resection of the prostate (TURP) for obstructive symptoms caused by BPH.

2.3 Rarely patients present with obstructive symptoms or urinary retention caused by tumor bulk. These symptoms are nonspecific and more indicative of benign prostatic hyperplasia than cancer as:

- 2.3.1 Decreased urinary stream.
- 2.3.2 Urgency.
- 2.3.3 Hesitancy.
- 2.3.4 Nocturia.
- 2.3.5 Incomplete bladder emptying.

2.4 Although rare in the current era of widespread screening, prostate cancer may also present with symptoms of metastases, such as:

- 2.4.1 bone pain,
- 2.4.2 pathologic fractures,
- 2.4.3 or symptoms caused by bone marrow involvement.

3. Diagnostic Work up:

3.1 Screening:

3.1 Screening for prostate cancer with prostate-specific antigen (PSA) testing remains controversial despite evidence that PSA testing reduces mortality. Prostate cancer mortality has decreased in the USA since the introduction of PSA testing in the early 1990s, and findings of the European Randomised Study of Screening for Prostate Cancer showed stable reductions in mortality for up to 13 years in the PSA-based screening group versus the control group.

3.2 PSA itself could be used as a risk stratifier. Although the American Cancer Society recommends a threshold of 2·5 ng/mL with screening every other year, below that level a more nuanced approach could be introduced using different cutoffs based on age, family history, and race. Giving up PSA screening would be taking a 20-year

step backwards in the prevention of prostate cancer-related death and might deny or scare off high-risk men who would clearly benefit from the protection. A targeted risk-based strategy of prostate cancer screening could be implemented today and could save lives while reducing harms compared with broad population-based screening.

3.3 PSA screening and DRE begins at the age of 50 years and to begin in the age of 40-45 if positive family history.

3.2 Daignostic Work Up:

3.2.1 Trans-rectal ultrasonography (for biopsy guidance)

Risk Group Assessment: Table A.2.a

Risk Group	T-stage	Gleason score	PSA level
Low	**T1-T2a**	**2-6**	**<10 ng/ml**
Intermediate	**T2b-T2c**	**7**	**10-20 ng/ml**
High (very high)	**T3A (T3b-T4)**	**8-10**	**>20 ng/ml**

3.2.2 Routine:

3.2.2.1 Clinical history and clinical examination
3.2.2.2 Rectal examination
3.2.2.3 Assessment of IPSS score
3.2.2.4 Assessment of SHAMS score

3.2.3 Laboratory:

3.2.3.1 Complet blood cell count, blood chemistry
3.2.3.2 Serum PSA (total, free, percentage free)
3.2.3.3 Plasma acid phosphatases (prostatic/total)
3.2.3.4 Serum Testosterone.

3.2.4 Radiographic imaging:

3.2.4.1 Magnetic resonance imaging
3.2.4.2 Radioisotope bone scan (PSA >20)
3.2.4.3 Computed tomography of pelvis
3.2.4.4 Chest radiograph (high risk for metastatic disease)

4. Staging TNM:

According to the American Joint Committee on Cancer Staging manual, 7th edition, 2010.

5. Prognostic factors:

The major predictors of the extent of disease for men with localized prostate cancer are:

5.1 Clinical stage.
5.2 Gleason score (GS).
5.3 Pretreatment PSA.
5.4 Perineural invasion.

5.5 The percentage of positive biopsies.

NB: Pretreatment levl of PSA is important predictor of PSA failure, whereas GS, T stage, and age are the more important predictors of survival.

6. Treatment:

6.1 Surgery (Radical prostatectomy):

There are four main types or techniques of radical prostatectomy

6.1.1. Retro-pubic radical prostatectomy.

6.1.2 Laparoscopic prostatectomy.

6.1.3 Robotic surgery.

6.1.4 Perineal prostatectomy.

- Radical prostatectomy remains one of the best options for selected cases.
- Impotence and incontinence are the main side effects.
- Outcome is less good with extra capsular extension (ECE), positive margins and Seminal vesicle invasion.
- There is no need for hormone ablation treatment with prostatectomy.
- Nerve sparing surgery is indicated to preserve the sexual function.

6.2 Watchful waiting

Indicated in patients with the following criteria:

6.2.1 Age > 70 or life expectancy < 10-15 years

6.2.2 Gleason ≤ 6

6.2.3 Minimal DRE findings

6.2.4 Slowly increasing PSA (< 1 ng/mL per year)

6.3 Treatment algorithm:

Issues to be considered before instituting treatment:

6.3.1 Age, comorbidities and life expectancy

6.3.2 Side effects of the treatments offered

6.3.3 Risk group (T-stage, PSA and Gleason score)

6.3.3.1 **Low risk:**

6.3.3.1.1 Life expectancy < 10 years

- Watchful waiting
- External beam radiotherapy
- Brachytherapy (currently not available in referral center)

6.3.3.1.2 Life expectancy > 10 years

- Watchful waiting (Usually discouraged before age 65)
- External beam radiotherapy
- Brachytherapy (currently not available in referral center)
- Radical prostatectomy ± pelvic LN dissection

*6.3.3.2 **Intermediate risk:***

6.3.3.2.1 Life expectancy < 10 years

- Watchful waiting
- External beam radiotherapy ± neoadj and concomitant hormones
- Boost brachytherapy can be added (currently not available in referral center)

6.3.3.2.2 Life expectancy > 10 years

- External beam radiotherapy ± neoadj and concomitant hormones
- Radical prostatectomy + pelvic LN dissection (except if calculated risk of LN involvement < 3%)

6.3.3.3 High risk:

- Neoadjuvant hormones then concomitant hormones +Radiotherapy + 2-3 year hormones.
- Radical prostatectomy + pelvic LN dissection
  → Only if small volume, no evidence of fixation or ECE
- Indications for adjuvant radiation post-prostatectomy:
  ECE, SV invasion and positive margins

7. Radiotherapy Protocol:

- Increased dose above 70 Gy increases control, but also increases toxicity.
- The benefit is mainly seen in intermediate and high-risk groups.
- Two to three years of hormone therapy vs. no HT increase OS in high-risk Patients.

7.1 External Beam: Planning Technique

7.1.1 Patient's preparation :

The day before simulation

The rectum should be empty for treatment as a full rectum also leads to greater variation in prostate position so patients should be advised on a Low residue diet and laxatives.

7.1.2 Immobilization:

- Patients undergoing conformal radiotherapy are planned and treated lying supine with arms above the head.
- Supine with knee support and box between the knees.
- CT scan with 3 mm cuts and IV contrast if needed.

7.1.3 Orientation, set-up, marking and reference points:

7.1.3.1 Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
7.1.3.2 Permanent ink (or tattoo) is applied to the lateral and midline reference points.

7.1.4 Image acquisition:

7.1.4.1 CT simulation

- For radical prostatic radiation the volume scanned should extend from the mid sacroiliac joint to 1 cm below the anus/ischium to include the prostate, seminal vesicles, rectum and bladder, and is extended superiorly to L3 if the pelvic lymph nodes are to be treated.
- CT examination will be performed on a four-detector spiral CT scanner using a slice thickness of 3-5 mm. IV contrast may be given upon request of the referring radiation oncologist. No oral or rectal contrast is used.
- Intravenous contrast may aid delineation of the pelvic lymph nodes. At the time of the planning CT scan, the size of the rectum and bladder should be assessed, the scan should be repeated after implementing the bladder and rectal protocols until the desired parameters are met.
- CT data are then transferred to the radiotherapy planning system for outlining and target volume definition. To improve target definition, MRI scans of the pelvis can be incorporated into radiotherapy planning protocols. Outlining studies have shown that the size of the prostate is overestimated on CT compared with MRI, which defines the apex of the prostate better CT-MRI image is helpful in determining the prostatic apex.

7.1.4.2 Simulator

For palliation, treatment volumes can be defined in the simulator. The GTV is defined from CT information and the clinical assessment.

7.1.5 Target definition:

7.1.5.1 GTV:

Is is not easy to define the GTV accurately with the current imaging techniques. So, the standard practice is to define the CTV.

7.1.5.2 CTV:

7.1.5.2.1 Low risk

- CTV to include prostate to a dose of 76 Gy.
- PTV = CTV 76+10 mm all around except posteriorly 8 mm.

7.1.5.2.2 Intermediate risk and High risk cancer prostate

- Phase I is CTV60 to include prostate and median 2 cm of seminal vesicles and **any extension of the primary tumor as determined by clinical or radiological examination** to a dose of 60 Gy.

- Phase II is CTV 76 to include the prostate only to 16 Gy.
- In case of invasion of the SV, the whole SV should be included in CTV 66.
- In case of periprostatic extension, the area of infiltration should be covered in the CTV 60.
- PTV 60 =CTV 60+ 10 mm all around except posterior 8 mm.
- PTV 76 =CTV 76 + 10 mm all around except posterior 8mm.

7.1.5.2.3 Lymph node involvement

Phase I Pelvis and prostate

- CTV T 46= Prostate and SV.
- CTV N 46 = Lymph nodes areas.
- PTV TN 46 = CTV T 46 +10 mm sup/inf/right/left/ant and 8 mm post+ CTV N 46 +7 mm.

Phase II Prostate + SV

- CTV T 60 + Prostate + SV.
- PTV 60 + CTV T 60 + 10 mm sup/inf/right/left/ant and 8 mm post.

Phase 3 Prostate

- CTV T 76 = Prostate only.
- PTV 76 = CTV T 74 + 10 mm sup/inf/right/left/ant and 8 mm post.

7.1.5.2.4 Prostatic bed

- CTV66
  - **Inferior border**

5 mm cranial to superior border of the penile bulb.

  - **Anterior border**

Posterior aspect of symphysis pubis (2 cm above the vesico - urethral anastomosis).

Posterior 1/3 of bladder wall (2 cm above the anastomosis).

  - **Posterior border**

Anterior rectal wall.

  - **Lateral border**

Medial border of obturator internus and levator ani muscles.

  - **Superior border**

Base of the SV if uninvolved and risk less than15 per cent.

Distal ends of SV if involved or risk more than15 per cent.

Include all the bladder neck, remnant SVs and surgical clips.

The PTV is the CTV + 10 mm isotropically except posterior 8 mm.

7.1.6 Technique:

7.1.6.1 Three dimentional conformal radiotherapy.
7.1.6.2 IMRT: Kindly refer to IMRT protocol.

7.1.7 Beam Arrangement:

5 fields (one anterior and 2 wedged lateral and 2 wedged antero-obliques) were used to cover the target volume.

7.1.8 Beam energies:

Photon beam 18 mv or 6 mv or mix of both.

7.1.9 Dose prescription and fractionation

7.1.9.1 Low risk:

- 76 Gy in 38 fractions to the PTV

7.1.9.2 Intermediate risk:

- 60 Gy in 30 fractions to the PTV
- 16Gy in 8 fractions

7.1.9.3 High risk:

- As intermediate risk.
- If SV involved phase I 66 Gy in 33 fractions to PTV and phase II 10 Gy in 5 fractions.
- But if whole pelvis radiotherapy is indicated.
  - 46Gy in 23 fractions whole pelvis.
  - 20 Gy in 10 fractions to the prostate and seminal vesicles.
  - 10 Gy in 5 fractions prostate only.

7.1.9.4 Post-operative radiotherapy:

- 60 Gy in 30 fractions immediately post-op
- 66 Gy in 33 fractions on rising PSA

7.1.9.5 Palliative radiotherapy

- 30 Gy in 10 fractions of 3 Gy per fraction given in 2 weeks.
- 20 Gy in 5 fractions of 4 Gy per fraction given in 1 week.

7.1.10 Dose limitation to OAR:

As per QUANTEC recommendation:

7.1.10.1 Penile bulb: mean dose to 95 % of the gland < 50 Gy.
7.1.10.2 Femoral heads: D100< 52 Gy.
7.1.10.3 Small bowel: V45< 195 cc.
7.1.10.4 Bladder: V 65 < 50 %
V75 Gy< 25%
7.1.10.5 Rectum: V50 Gy<50 %
V70 Gy<25%

7.1.11 Verification:

- The treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is _5 mm.

7.2 Brachytherapy:

7.2.1 Introduction:

- In general, brachytherapy alone is used for tumors clinically staged as T1 and T2a, whereas stage T2b and T2c lesions with high risk of extra capsular extension and pelvic node metastases are usually treated by a combination of external irradiation and brachytherapy.
- HDR and LDR brachytherapy may be used as a boost after EBRT to escalate dose to the prostate.

7.2.2 Indications for brachytherapy:

- Life expectancy >10 years.
- Biopsy-confirmed adenocarcinoma prostate
- Low risk disease: T1–T2a, PSA less than 10, GS 6
- Intermediate risk disease: T1–T2a, PSA less than15, GS 3 + 4 (low volume).
- Prostate volume < 50 mL (dynamic techniques can treat up to 90 mL).
- It is important to select patients with no significant urinary outflow obstruction since they are at increased risk of urinary retention and morbidity following brachytherapy.
- Ideally patients should have an international prostate symptom score (IPSS) of <12 and urine flow rate Qmax of >15 mL/s.

7.2.3 Methods:

- **Permenant LDR implant or HDR, currrently brachytherapy is not available at referral center.**

7.3 Sequelae of treatment

All toxicities are assessed and scored according to RTOG/EORTC toxicity criteria.

7.3.1 Acute: Dysuria, (commonest), urgency, frequency, nocturia, urinary retention. diarrhea, Rectal irritation, pain, bleeding and fatigue.

7.3.2 Late: Urinary stricture less than 4%, rectal bleeding 5-10%. NB: Gynecomastia can occur due to the use of antiandrogens.

8. Principle of hormonal treatment:

- Androgen deprivation therapy (ADT) is administered as primary systemic therapy in advanced disease or as Neoadjuvant or concomitant or adjuvant therapy in

combination of radiotherapy in locally advanced disease. Casterate level of serum testosterone should be achieved, because low levels of serum testosterone levels were shown to be associated with improved cause specific survival.

- ADT can be surgical casteration or medical casteration (use of lutinizing hormone releasing hormone agonist or antagonist.
- Antiandrogen therapy should precede or coadminesterd with LHRH agonist for at least 7 days to diminish ligand binding to androgen receptor.

9. Principles of chemotherapy:

- Recent research has expanded the therapeutic options for patients with metastatic casteration resistanse prostate cancer (CRPC)
- Decetaxel is included as an upfront option foe men with progressive androgen stinulated prostate cancer and distant mets based on ECOG 3805/CHAARTED and STAMPEDE trials.

10. Management of relapse:

Biochemical failure is only a surrogate for other more solid end-point

10.1 Failure post-prostatectomy

- After RP, PSA should be undetectable.
- PSA that never falls to undetectable levels → Systemic disease is assumed.
- If PSA rises > 0.2 after being undetectable → PSA failure
  → A local relapse is assumed.

10.1.1 Risk factors for increased probability and decreased time to metastatic disease:

- High Gleason score
- Biochemical failure < 2 years
- PSA doubling time < 10 months

10.1.2 PSA doubling time after treatment:

- Surrogate marker for **metastasis-free survival** and **prostate specific surA doubling time < 3 months** predicts worse prostate specific survival.

10.2 Treatment options at relapse:

10.2.1 Observation.
10.2.2 Hormonal therapy.

10.2.2.1 Early versus delayed hormonal treatment:

- Studies comparing **early** or **late** hormones done in the metastatic setting only: → **Early hormonal treatment is better for locally advanced or metastatic disease.**
- Intermittent versus continuous hormonal treatment:
  It applies only to the PSA relapse setting.

- Hormones given until maximal PSA response.

- Treatment stopped at restarted at a preset PSA level (5-20).

10.2.2.2 Treatment of progressing PSA in the setting of hormonal treatment:

- LHRH agonist can be either continued or removed
- Rationale for continuing or restarting it when testosterone levels increase.
- Subpopulation is still sensitive to testosterone.
- Antiandrogen can be added.
- Mutations in Androgen Receptors might cause paradoxical stimulation by antiandrogens
- Other drugs can be used:
  - Ketoconazole → Inhibits steroidogenesis
  - Prednisone

10.2.2.3 Hormonal therapy for CRPC

Most men with advanced disease eventually stop responding to traditional ADT are catecorized as casteration resistance. Androgen signalling from non gonadal sources in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents (Abiraterone acetate – Enzalutamide) demonstrating efficacy in metastatic CRPC setting dramatically changed the paradigm of CRPC.

10.2.3 Salvage RT after RP:

- Considered if disease is localized to tumor bed only.
- Positive surgical margins.
- Seminal vesicle invasion.
- PSA doubling time < 10 months.
- Pre-RT PSA > 2.0.

ASTRO Recommendation:

- Treated patients should not have metastatic disease.
- Treatment should be instituted before PSA > 1.5.
- Dose should be higher than 64 Gy.

10.2.4 Salvage RP after RT.

- Not very popular due to technical difficulty and side effects.
- Complication rate of 50%.
  - Rectal injury 10%.
  - Bladder neck contracture 25%.
  - Haemorrhage 5%.
  - Ureter injury 55.
  - DVT, PE.
  - Chronic urinary incontinence 45%.
- Can be considered in patients with:
  - localized disease.

- Original low risk disease.
- Gleason < 6, T1c or T2a.
- PSA < 4 at recurrence.

10.2.5 Cryotherapy after RT.

10.2.6 Chemotherapy in metastatic disease:

Response to chemotherapy is assessed by:

- Objective response, if soft tissue lesions are visible.
- Survival.
- PSA decrease by at least 50%, confirmed by a second PSA.
- Mitoxantrone + steroids better than steroids alone.
  - As per several randomized controlled trials.
  - OS of 1 year, but symptomatic control is better.
- Docetaxel + prednisone better than mitoxantrone + steroids
  - Docetaxel q 3 weeks
  - OS increased to 18 months
- Chemotherapy for prostate ca with low PSA
  - Neuroendocrine features (small cell)
  - Poorly differentiated prostate adenocarcinoma

11. Follow Up:

11.1 Weekly follou up during radiotherapy for assessment of toxicities.

11.2 Follow up of cases after completion of treatment will be through history, clinical examination, the PSA and the imaging when indicated according to the patient's symptoms and signs or PSA level.

12. Ongoing Departmental Studies:

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A.3- SUPERFICIAL BLADDER CANCER CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

1.1 Approximately 70-80% of newly diagnosed bladder cancer cases are classified as superficial or non-muscle-invasive. This category of bladder cancer includes Ta (papillary), T1 (that invade the lamina propria but do not extend into the superficial muscles layers) tumors, and Tis (carcinoma in situ, CIS) which account for approximately 70, 20 & 10% of superficial or non-muscle invasive cancers, respectively. The majority are transitional bladder tumours of various histologic grades (I – III). Superficial tumours are single in 70% and multiple in 30%. About 30% of superficial tumours turns into invasive tumours.

2. Clinical Presentation:

2.1 Painless gross hematuria (90%).
2.2 Dysuria.
2.3 Frequency of micturition.
2.4 Pain under the umbilicus in bladder region.
2. 5 Recurrent urinary tract infections

3. Diagnostic work-up after TUR:

3.1 History & Physical examination.
3.2 Investigations:
- 3.2.1 CBC, Biochemistry profile
- 3.2.2 Review of initial Cystoscopy & advise for 2nd look Cystoscopy in T1G3 cases if not done.
- 3.2.3 Review of histopathology at referral center.

Following TUR, after initial work up patient is planned for follow up/ intra-vesical Mitomycin/ BCG as per indication

4. Staging

No specific staging all Ta, T1 & CIS bladder lesions are labelled as superficial bladder cancer.

5. Prognostic factors:

5.1 Tumour size and grade.
5.2. Multifocality.
5.3 Positive post-operative urine cytology.
5.4 Prostatic urethral involvement.
5.5 The presence of CIS, and tumours that invade the lamina propria.

6. Treatment:

6.1.1 The initial treatment of superficial or non muscle invasive bladder cancers generally is a complete cystoscopic (transurethral) resection of all visible bladder tumor (TURBT). It should also provide selective biopsies of the remaining bladder, mapping of the sites of tumour and elective biopsies and also provide barbotage sample for cytology. This is often followed by adjuvant intra-vesical therapy because many patients with superficial bladder cancer treated with endoscopic surgery alone have recurrence or tumour progression at some point in their follow up, and in these patients, the need for adjuvant intra-vesical treatment becomes a major concern.

6.1.2 Today, the use of intra-vesical chemotherapy for superficial bladder cancer has become more generally accepted. The main goals of intra-vesical chemotherapy for superficial bladder cancer are to prevent tumour recurrence or tumour progression after TUR and to treat possible residual tumours after endoscopic surgery. The identification of patients with superficial bladder tumours **who are at risk for** tumour recurrence and tumour progression after surgical treatment is very important in the selection of candidates for adjuvant or prophylactic use of intra-vesical therapy.

6.1.3 Several anti-tumour agents with definitive activity against CIS or residual tumours after TUR are available. The most commonly studied are, doxorubicin, mitomycin C, epirubicin and the non-chemotherapy BCG.

6.1.4 The ideal drug for intra-vesical therapy would be inexpensive and would have minimal systemic absorption and local toxicity while effectively preventing tumor recurrence and progression after TUR of the primary tumour.

6.2 Indications for Intra-vesical therapy:

6.2.1 All patients with high grade pTa, T1 and CIS lesions

6.2.2 Its optional in patients with totally resected pTa low grade lesions.

6.2.3 Therapeutic use intra-vesical chemotherapy for eradicating post TURB residual tumors.

6.2.4 Intra-vesical chemotherapy is also used when BCG is not effective or when the side effects of BCG are intolerable.

6.3 Bascillus-Calmette-Guerin (BCG):

- BCG has emerged as an important intra-vesical agent because of its economy and effectiveness in prophylaxis against tumour recurrence after TUR of the primary and in the treatment of residual tumours. In patients with CIS, BCG immunotherapy achieves a 70% response rate on average and it has replaced cystectomy as the initial treatment of choice for CIS. Controlled clinical trials suggest that BCG immunotherapy reduces disease progression, decreases the need for cystectomy and prolongs survival. A reduction in percentage of recurrences of 7-65% is seen in reviewed studies, and all them are statistically significant. When compared with other commonly used intravescial chemotherapeutic agents, only with Mitomycin C has the advantage of BCG not be clearly apparent.

- The efficacy of BCG has been confirmed with multiple BCG preparations, doses and treatment schedules.
- The administration involves diluting the BCG in 50cc of normal saline and instillation within the bladder to be held for 2 hours weekly for 6 weeks followed by maintenance therapy i.e.3 weekly applications at 3 & 6 months followed by every 6 months x 3.
- Nevertheless, the toxicity and side effects of intravesical BCG therapy cannot be ignored. Dysuria and urinary frequency occur in about 90% for patients. Approximately 24% of patients have fever, and 18% and 8% have malaise and nausea respectively.
- Anti-tuberculosis therapy is required in as many as 6% of patients treated due to severe side effects. For patients who do not appear to be tolerating the standard dose of BCG, the dose can be reduced by half, and isoniazid 300 mg can be given.
- In those with evidence of BCG infection, such as epididymitis, hepatitis or symptomatic prostatitis, isoniazid plus rifampin 600 mg are used. The most dangerous complication of BCG is systemic septic or hypersensitivity reaction, which has been estimated to occur in 1:15,000 patients. This can be controlled by adding prednisone 40 mg daily to INH and rifampin. Anti-TB medication is continued for 3-6 months.

6.4 Mitomycin C:

- Mitomycin C is an alkylating agent with a molecular weight of 334 kd. It acts by binding to DNA resulting in synthesis inhibition and strand breakage. MMC has been used in various schedules for intravesical therapy.
- Doses range from 20-60 mg diluted in water at concentrations between 0.5-2.0 mg/ml, with bladder dwell times between 1-2 hours. Optimal dosing schemes for intra-vesical therapy have not been established, but at least 6 weekly instillations are used most often and probably represent an adequate course.
- There is some evidence that maintenance therapy may be helpful and additional treatments may be considered in patients with high risk features such as high grade or multiple T1 tumours.
- Because of its high molecular weight, absorption of MMC into the systemic circulation is low, and systemic reactions are not common.
- The most common local side effects are dysuria and urinary frequency, occurring in as many as 41%. Allergic reactions in 3-19% and reduced bladder capacity have been seen. Leukopenia and thrombocytopenia are uncommon.

6.5 Cystectomy for Superficial Bladder Cancer:

Some patients with CIS or T1 tumors who may be considered at increased risk of recurrence and/or progression may be the candidates for initial cystectomy. High risk factors include:

6.5.1 Large tumor.
6.5.2 High grade.
6.5.3 Tumor location in a site poorly accessible to complete resection.
6.5.4 Diffuse disease.
6.5.5 Infiltration of lymphatic or vascular spaces.
6.5.6 Prostatic urethral involvement.

6.5.6 CIS or high grade T1 that have persisted or recurred after initial intra-vesical treatment.

6.6 Administration of Intra-vesical therapy

Some basic principles should be followed when administering intravesical chemotherapy.

6.6.1 Distilled water is the preferred solution for drug dilution.

6.6.2 The bladder should be emptied immediately before drug instillation.

6.6.3 The patient should avoid excessive fluid intake to prevent dilution of the agent.

6.6.3 Following instillation, the patient should hold urine for 1 to 2 hours.

6.6.4 Treatment should preferably start early (within 15 days) of TUR.

6.6.5 Urethral trauma secondary to catheterization is uncommon, but if trauma is considerable treatment should be postponed. Because urethral catheterization in the presence of infected urine may cause systemic complications, a urinalysis should be performed before instillation.

6.7 Practical guidelines for intra-vesical Mitomycin instillation:

It is a very safe procedure with minimal local side effects & practically no systemic toxicity.

6.7.1 Guidelines for pharmacist:

- Preparation is preferred in an empty, biohazard laminar down flow unit but can be prepared in office.
- Avoid contamination of hands & eyes.
- Reconstitute in 50 ml diluent.
- Dilution container (syringes with lock, plastic bags, and glass bottles).
- Avoid exposure to light.

6.7.2 Guidelines for Physician & Nursing staff:

- Six hrs after TURBT for single instillation OR with 1-2 wks after TURBT.
- Culture and sensitivity of the urine, and treat urinary infection before instillation.
- Assess bladder capacity before instillation. Instillation to be kept a minimum of 1 hr or as long as patient can tolerate.
- In case of over active bladder, use a balloon catheter connected with a bag containing Mitomycin at 20 cm above the bladder level.
- Ask the patient to void before the procedure or empty the bladder by catheterization, lubricant can be used.
- Empty catheter and wash it with 2 ml saline.

6.7.3 Instructions for the patients:

- Keep instilled Mitomycin for 1-2 hrs.
- Keep changing position while in bed.
- Avoid contamination of hands while voiding.
- Sexual relations – Avoid sexual relation for 24 hrs after instillation.

6.8 Practical guidelines for intra-vesical BCG instillation:

Always remember that live attenuated bacilli have virulent properties and can cause systemic infection if not used properly. The following must be kept in mind:

6.8.1 Absolute contra-indication for BCG.

- Not within 2 weeks from TUR / biopsy.
- Active tuberculosis.
- Immunocompromised patients (congenital immunodeficiency, acquired immunodeficiency syndromes including HIV positive without clinical manifestations.
- Systemic immunosuppressive treatments.
- Organ transplant recipients.
- Myeloproliferative syndromes.
- Hodgkin's disease.
- Pregnancy & lactation.
- Uncontrolled urinary tract infections.
- Systemic complications because of previous BCG treatments.

6.8.2 Relative contra-indication for BCG:

- Concomitant administration of anti-coagulants & antibiotics.
- Micro haematuria.
- Leucocytopenia.
- Transient urinary tract infection until treated.
- NB: A mild degree of vesico-uretheral reflux is not considered a contra-indication.

6.8.3 Guidelines for the Pharmacist:

- Strains contained in vials are preferred (less risk for break, spillage & reduced doses possible).
- Preparation preferred in an empty, biohazard, laminar down flow unit.
- Avoid contaminating large area of the laboratory.
- Precautions to avoid infection (wear mask, gloves and check hands for wounds).
- Reconstitute with 2 ml of given diluent. Swirl vial gently.
- Empty in a container (syringes, plastic bags or glass bottles) and dilute it with 50 ml of preservative free normal saline. Syringes with luer lock connection are preferred to reduce the risk of spillage.
- Preparation should be immediately before instillation.
- Aggregation occurs after 15 min at room temprature (aggregation does not affect viability but influence anti-tumor activity).
- Do not attempt to remove aggregates by infiltration.
- Reduce aggregation by eliminating liquid / gas interface.
- Dispose all material as infectious waste.
- Disinfect laminar flow unit with 96% alcohol.

6.8.4 Guidelines for Physician & Nursing staff:

Ensure the absence of any contra-indications to BCG instillation.

- Urine C&S before instillation to exclude infection.

- Assess bladder capacity before instillation. The patient should be able to retain the BCG solution for 2 hours (optimal) to allow better contact for regulation of cytokine production.
- Instillation should be by gravity.
- In case of over – active bladder, insert a balloon catheter connected with a bag containing BCG solution at 20 cm above bladder level. Allow in & out flow.
- Avoid combining antibiotics with BCG (BCG is susceptible to more than 18 antibiotics).
- Avoid delay between preparation of BCG & its instillation. Optimal time is within 15 min.
- Empty bladder by gentle catheterization.
- Avoid excess lubricants (can decrease BCG vitality).
- Avoid injury to the urethra. Postpone the procedure if there is bleeding during catheterization as it can cause fatal sepsis.
- Avoid pressure while instillation, let it go with gravity.
- For females, a short catheter can be used.
- Empty catheter itself; flush it with 5-10 ml saline.
- All material to be disposed as infectious waste.
- Observe patient by the instillation / maintenance instillation for
  - Local symptoms, haematuria, urgency, dysuria.
  - Systemic symptoms, fever, arthralgia, pneumonitis, hepatitis.

6.8.5 Instructions for the patient:

- Keep instilled BCG for 2 hours (optimal).
- Void in sitting position for 24 hrs.
- Rinse toilet with disinfectant (Clorox) at least 50 ml after each urination.
- Keep disinfectant for 15-20 min & than flush.
- Wash hands thoroughly after voiding.
- Avoid sexual relation for 48 hrs after instillation.
- Use condom during instillation course.
- Check body temperature during day of instillation & one day after, inform if temperature is more than 38.5 C.

7. Radiotherapy Protocol:

Not Applicable

7.1 External beam

Not applicable

7.2 Brachytherapy

Not applicable

7.3 Sequelae of treatment

7.3.1 Intravesical BCG

7.3.1.1 Acute: dysuria, frequency of micturition (90%), Pain, burning in micturition, generalized weakness are common symptoms after the BCG.

7.3.1.2 Fever (24%), malaise (18%), Nausea (8%).
7.3.1.3 Anti-tuberculosis therapy is required in as many as 6% of patients treated due to severe side effects. For patients who do not appear to be tolerating the standard dose of BCG, the dose can be reduced by half, and isoniazid 300 mg can be given.
7.3.1.4 In those with evidence of BCG infection, such as epididymitis, hepatitis or symptomatic prostatitis, isoniazid plus rifampin 600 mg is used.
7.3.1.5 The most dangerous complication of BCG is systemic septic or hypersensitivity reaction, which has been estimated to occur in 1:15,000 patients. This can be controlled by adding prednisone 40 mg daily to INH and rifampin. Anti-TB medication is continued for 3-6 months.

7.3.2 Mitomycin C:

7.3.2.1 Dysuria and urinary frequency, occurring in as many as 41%.
7.3.2.2 Allergic reactions in 3-19% and reduced bladder capacity have been seen.
7.3.2.3 Leukopenia and thrombocytopenia are uncommon.
7.2.3.4 Late: recurrence or progression of disease

8. Principles of Hormonal Treatment:

Not Applicable

9. Principles of Chemotherapy:

Not Applicable

10. Management of Recurrence / Relapse:

10.1 Recurrent non-muscle invasive papillary tumors (Ta, (table 1) can generally be managed with repeat TURBT. It is even possible to safely monitor these patients initially and intervene when size or symptoms dictate in patients with an established Pattern of low-grade recurrences.
10.2 Tis (carcinoma in situ) can not be controlled with TURBT alone. If intra-vesical therapy fails to control disease, cystectomy is indicated.
10.3 T1 disease: Patients who relapse with recurrent T1 tumors within six months to one year after TURBT and one or two courses of BCG are best treateded with cystectomy.
10.4 Intra-vesical therapy with valrubicin or BCG plus interferon may avoid or delay cystectomy, particularly in patients who represent a poor medical risk.

11. Follow Up:

11.1 Blood tests, urine cytology and cycstoscopy before each maintainace dose of BCG.
11.2 Urine cytology every 3 months & Cystoscopy every 6 months for initial 2 years then yearly.

12. Ongoing Departmental studies:

Not Applicable

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A.4- INVASIVE BLADDER CANCER CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

Invasive Bladder cancer is the 4th most common cancer in men and the 8th in women. It occurs more frequently in males than females. It represents 5-10% of male cancers. The ASIR for Kuwaiti male & female is 9.3 & 1.9 as compared to 3.8 & 2.0 for non-Kuwaiti respectively. The ASIR is 4.5 & 1.2 for GCC & 9.0 & 2.2 for the world.

Cigarette smoking, Aniline dye, cyclophosphamide, pelvic radiation and Schistosoma haematobium infections (sp. in Egypt), Aromatic amines & Naphthylamine, Benzidine are known carcinogenic agents for the bladder. At least 50% of cases in males and 25% in females are causally related to cigarette smoking.

2. Clinical Presentation:

2.1 Painless gross hematuria (90%).

2.2 Dysuria.

2.3 Frequency of micturition.

2.4 Pain under the umbilicus in bladder region.

2.5 Recurrent urinary tract infections.

3. Diagnostic Work up:

3.1 History and clinical examination.

3.2 Investigations:

3.2.1 Full blood count, renal / liver function tests, & Creatinine Clearance. Urine analysis with urine cytologic study to detect the presence of suspicious cells.

3.2.2 A cystoscopic examination includes documentation on a bladder diagram of tumor location, number of lesions, pattern of growth, and tumor size (tmour mapping).

3.2.3 A transurethral resection of a bladder tumor (TURBT) is diagnostic and often therapeutic in superficial lesions. Muscle must be seen by the pathologist in a biopsy or transurethral resection for it to be an adequate indicator of prognosis.

3.2.4 Patients with muscle-invasive disease require a screening workup for metastatic disease that includes chest imaging by either computed tomography (CT) or plain films as well as pelvic imaging to identify nodal involvement using CT or magnetic resonance imaging (MRI) of the pelvis. Imaging should include the abdomen if there is pelvic nodal disease or abnormal results of liver biochemistry studies.

3.2.5 In patients with invasive or locally advanced disease or in patients with elevation of the serum alkaline phosphatase level or bone pain, a bone scan should be performed to rule out metastases.

3.2.6 Role of PET CT is still not yet well defined in initial evaluation of bladder cancers, it is considered on individualized basis.

3.2.7 After staging work-up is completed, the patient is discussed in the multidisciplinary GU group meeting including Onco-Surgeons, Radiation Oncologists, and Medical Oncologists.

4. Staging TNM:

According to the American Joint Committee on Cancer (AJCC), 2010, 7th edition.

5. Prognostic factors:

5.1 Depth of invasion and Grade of the tumor are the most important prognostic indicators.

5.2 Lympho-vascular invasion is significant, even in albescence of the positive lymph nodes and even if the tumor is confined to lamina propria.

5.3 Carcinoma in situ, solid tumor morphology, large tumors size, multiplicity of tumors, muscle invasion, histologically positive nodes, obstructive uropathy indicate poor prognosis.

5.4 Stage of the disease is the important prognostic factor. Metastatic disease at diagnosis carries poor outcome.

5.5 Performance status and associated co-morbid conditions are important indicators.

6. Treatment

6.1 General Management:

Treatment of urinary bladder cancer is a multidisciplinary management. Very early Cancer needs TUR and based on the histopathology and grade of the tumor further.

6.1.1 Muscle invasive tumors; the treatment options are

6.1.1.1 Radical cystectomy

6.1.1.2 Partial cystectomy

6.1.1.3 Bladder conserving surgery + Chemo-radiotherapy.

6.1.2 Tumors with no CIS in the dome of bladder may be treated with partial cystectomy.

6.2 The Gold standard is Radical cystectomy. Other options include:

6.2.1 TURB alone:

Done in early selected patients only with:

- Uni-focal T2a, grade 1 disease with no CIS and no evidence of a palpable mass or hydronephrosis.
- If repeat cystoscopy and cytology are negative. Close life long follow up, 60% rate of recurrence or new bladder tumor.

6.2.2 Partial cystectomy:

Indicated in:

- Well defined T1 and T2 tumors less than 6-8 cm.
- Located in a mobile area of the bladder: Dome
- No CIS on random biopsies.
- No involvement of the trigon.
- Expected good bladder function after resection with 2 cm margin.
- Negative margin is a must. Local recurrence of 40-80% depending on stage.
- OS similar to cystectomy for T1 and T2, but worse for others.

6.2.3 Radical cystectomy:

- Indicated in: Stage II, III as well as intractable superficial disease.
- Starts with a lymph node dissection and aborted if LN+ obturaotr and hypogastric nodes are resected. Bladder, prostate, seminal veiscles, proximal vase deference, 2 cm of proximal urethra, TAH BSO, anterior vaginal wall, 2 cm ureter and urethra, and margins in peritoneum and fatty tissue (anterior pelvic exentration).
- Urinary diversion: done with ileal conduit to skin or ileo-cecal pouch to skin.
- Side effects: sexual dysfunction and urinary incontinence, UTI, stenosis, stoma complications.

6.3 Radiotherapy alone:

6.3.1 Might have a role after partial cystectomy.
6.3.2 Role is very limited neoadjuvantly or adjuvantly to cystectomy.
6.3.3 Possibly for positive margins or positive LN.
6.3.4 Used for patients who refuse or cannot undergo surgery.
6.3.5 Palliatively for T3b and above (OS < 10%).
6.3.6 Curatively for T2-T3a although mainly a banded for CTRT.
6.3.7 Better response to RT if:

- T2-T3a
- Uni-focal (no in situ)
- No hydronephrosis
- No residual tumor post TURBT (10% v/s 70% LC)
- Tumor smaller than 5 cm
- Low grade

Neo-adjuvant chemotherapy may be considered to improve outcome.

6.4 Bladder preservation treatment:

- Complete response rates of the primary tumor:
  - RT alone: 35-55%
  - CT alone: 11-37%
  - TURBT+ CT 45-61%

- TURBT+RT+CT 64-87%

6.4.1 Bladder preservation by:

- Aggressive TURB: complete resection of the disease.
- Induction Radiotherapy+chemotherapy (RT+CT): radiosenstization.
- Cystoscopic evaluation at 40 Gy.
- If PR then radical cystectomy.
- If CR (Ta or Tis) more RT+ CT.

6.4.2 Outcome:

- Never compared head to head with cystectomy
- 5 year OS of 50%
- Complete response at cystscopy with biopsy : 75%
- Higher with visible complete resection at TURBT
- Higher with clinical stage T2-T3 a
- Higher if no hydronephrosis is present.
- Of the complete responders, 15% recur with invasive disease.
- Of the complete responders, 25% recur with non-invasive disease.
- Thus, of the complete responders, 60% did not fail in the bladder
- Distant metastasis rate of 30%.

6.4.3 Indications for bladder sparing or conserving surgery protocols:

6.4.3.1 Ideally, T2-T3a
6.4.3.2 Tumor < 5 cm
6.4.3.3 No ureteric obstruction no hydronephrosis.
6.4.3.4 Good bladder function
6.4.3.5 Visibly complete TURB.
6.4.3.6 In reality, T2-T4a with maximum TURBT is acceptable.

7. Radiotherapy Protocol

7.1 External Beam: Planning technique

7.1.1 Patient preparation

7.1.1.1 The day before simulation

- Patient should avoid eating large amount of fruits and vegetables, beans and dairy products.

7.1.1.2 The day of simulation

- Patient should eat light meals before simulation. Patient may take a fleet enema. He/she may take this at home or wait until coming to the radiation treatment centre.
- Patient should drink 500 cc of plan water before simulation to make bladder full (at least 70%).

- Repeat this bladder filling process before each of daily radiation treatments.
- After the first few treatment days, patient will learn what works best for him/her- how much water to drink and over what period of time.

7.1.2 Immobilization:

- Patients undergoing conformal radiotherapy are planned and treated lying supine with arms above the head.

7.1.3 Orientation, set-up, marking and reference points:

- Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points

7.1.4 Image Acquisition:

- **CT simulation**

For conservative bladder radiation the volume scanned should extend from L5 to S1 superiorly to the ischium inferiorly. CT examination will be performed on a four-detector spiral CT scanner using a slice thickness of 3-5 mm. IV contrast may be given upon request of the referring radiation oncologist.

- **Simulator**

For palliation, treatment volumes can be defined in the simulator. The patient lies supine. The GTV is defined from CT information.

7.1.5 Target definition:

7.1.5.1 GTV: Gross tumor volume, as seen on CT and cystoscopy mapping.
7.1.5.2 CTV I: (GTV + whole bladder + 5mm) + prostate + lower external and internal iliac LNs.
7.1.5.3 CTV II: GTV+ whole bladder + 5 mm.
7.1.5.4 PTV: CTV + 1.5-2 cm (7 mm on lymph nodes only).

7.1.6 Technique:

Three dimentional conformal radiotherapy.

7.1.7 Beam arrangement

Usually Four fields radiation beam or as per Plan.

7.1.8 Beam Energies

10 – 18 Mv as per plan

7.1.9 Dose prescription and fractionation

7.1.9.1 Radical radiotherapy: Total dose to be delivered: Total 66 Gy.

- 46 Gy in 23 fractions of 2 Gy in phase I

- 20Gy in 10 fractions in phase II

7.1.9.2 Palliative radiotherapy

- 30 Gy in 10 fractions of 3 Gy given in 2 weeks.
- 20 Gy in 5 fractions of 4 Gy given in 1 week.

7.1.10 Dose limits to OAR:

Refer to cervix protocol for female and prostate protocol for male patients.

7.1.11 Verification and plan execution

7.1.11.1 The treatment isocenter on a DRR from the CT simulation is compared with portal images of the isocenter on the treatment machines using electronic portal imaging.

7.1.11.2 Off-line correction protocols are used for standard conformal treatment.

7.1.11.3 Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is ± 5 mm.

7.2 Brachytherapy

Not Applicable

7.3 Sequelae of treatment

7.3.1 Acute adverse side effects: pruritis, loss of pubic hair, dry, moist desquamation, reddening and irritation of the skin in irradiated filed, nausea, colitis, cystitis, vaginitis, tiredness near the end of treatment, diarrhea, rectal irritation, urinary frequency and dysuria and depression of the blood counts.

7.3.2 Late: reduced bladder capacity, urethral stricture (1-3%), vesico-vaginal fistula, intestinal obstruction or perforation (less than 5%) femoral neck fracture (less than 5%).

8. Principles of Hormonal Treatment:

Not Applicable

9. Principles of Chemotherapy :

9.1 Adjuvant:

- No role for chemotherapy adjuvantly to a cystectomy.
- It might be considered in high risk patients to improve DFS but not OS.
- pT3 and LN+, as long as it is well discussed with patients.

- MVAC or CMV should be used.
  Cispaltin, Vinblastin, methotrexate +- doxorubicin.

9.2 Neoadjuvant chemotherapy:

- The largest neoadjuvant trials have used standard MVAC or CMV for 3cycles.
- Single agent cispaltin is not recommended because it was proven inferior to MVAC.

9.3 Palliative chemotherapy:

- Dose intense MVAC with G-CSF or GC (gemicitabine –cispaltin).
- MVAC has similar effects but more side effects.
- CMV is slightly less effective but can be used.

10 . Management of Recurrence / Relapse/metastases

- Although systemic chemotherapy is the principal treatment for recurrent or metastatic transitional cell carcinoma, radiation therapy frequently provides excellent control of localized symptoms. Typically, these symptoms include pelvic pain, obstruction, and haemorrhage or extremity oedema. Patients with recurrent bladder tumors, however are likely to be elderly, severely symptomatic and also may suffer from substantial co-morbid conditions. Therefore, palliation must be individualised.

- A short course of 30 Gy/10 fractions of local pelvic radiotherapy may be effective in alleviating **symptoms of local recurrence** for short term. Even a very short course of 20 Gy/5 fractions can be delivered in very advanced locally recurrent tumours. For a locally advanced bladder tumour with haematuria, the patient can be given a haemostatic dose of radiotherapy to the bladder area (dose 12 Gy/3 fr or even a single fraction of 6 Gy). Here the dose to the only diseased site i.e. bladder only will be suffice.

- For **bony metastases**, radiation offers excellent short term pain relief. Radiation relives pain from bony metastases in more than 70% patients and should be considered following orthopaedic stabilization for impending pathologic fracture.

- **Spinal cord compression or Cauda equina syndrome** benefits from early diagnosis and treatment. Dose: 30 Gy/10 fractions.

- **Solitary brain metastases** from TCC can be treated with stereotactic radiation or with combination of surgery or post operative radiotherapy. Whole brain radiation can be offered to such patients and dose of 30 Gy/10 fr or 20 Gy/5 fr along with steroids and other supportive medications are to be given.

11. Follow Up

11.1 Weekly during radiotherapy for assessment of toxcicty.
11.2 3-6 weeks after completing radiotherapy for toxicity assessment.
11.3 Every 3 months for 1 to 2 years after compeleting RT, then every 6 months for 3 to 4 years, and annually after 5 years.
11.4 Close clinical examination and cystoscopy to exclude local recurrence / new primary tumors.
11.5 CT and or MR imaging as clinically indicated.

12. On Going Departmental studies

Not Applicable

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A.5- TESTICULAR CANCER CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

Testicular tumors represent the most common malignancy in men in 15 to 35 years of age, the majority of primary neoplasm's of the testis arise from germinal elements, accounting for 90 to 95 percent of all testicular neoplasms.

The germinal neoplasms are classified as seminomatous & non-seminomatous germ cell tumors. The ASIR is 1.5 for the World and 0.7 for GCC. The ASIR for Kuwaiti male is 2.0 as compared to 0.5 for Non-Kuwaiti. The Peak incidence of testicular tumors occurs in late adolescence to early adulthood (20-40 years), non-seminomatous neoplasms occur in relatively younger males as compared to seminomatous tumors.

2. Clinical Presentation:

2.1 Commonest presentation is painless swelling in the scrotum. Pure seminoma confined to testis (84% with stage I) spreads orderly to retro-peritoneal lymph nodes (13% stage II).

2.2 Mediastinum and supraclavicular are next echelon (stage III). Less than 5% are stage III or IV at presentation.

3. Diagnostic Work up:

3.1 History:

Information regarding previous scrotal or inguinal surgery, mal-descent, retractile testis and orchiopexy.

3.2 Physical examination:

3.2.1 Special attention to possible site of lymph node metastases i.e. abdomen and both supraclavicular area.

3.2.2. Contralateral testis should be examined.

3.3 Laboratory studies:

3.3.1 CBC, Electrolytes, LFT and RFT.

3.3.2 S.βHCG and S.AFP

3.3.3 Semen analysis.

3.3.4 Sperm banking if the quality is adequate for patient in whom treatment is likely to compromise fertility and patient desires child in future.

3.4 Radiological investigations:

3.4.1 X-ray chest.

3.4.2 Ultrasound of the testis.

3.4.3 CT scan of abdomen and pelvis.

4. Staging TNM:

The American Joint Committee on Cancer (AJCC), 7th edition, 2010.

5. Prognostic Factors:

5.1 Tumor size > 4 cms,

5.2 Lympho -vascular invasion

6. Treatment

The appropriate surgical procedure to make the diagnosis and remove the primary tumor is a radical orchiectomy through an inguinal excision with high ligation of spermatic cord.

6.1 Stage I

6.1.1 Surgery + External radiotherapy to para-aortic and ipsilateral pelvic lymph nodes.

6.1.2 If patient wants to preserve fertility options are:

- Irradiation to para-aortic lymph nodes only.
- One course of chemotherapy.

6.1.3 If patient refuses chemotherapy and radiotherapy, unmarried and is low risk, i.e. classical, spermatocytic seminoma, surveillance can be considered.

6.2 Stage II-A:

6.2.1 Same radiotherapy field as Stage I, but to encompass the lymph nodes.

6.3 Stage II-B:

6.3.1 Most receive chemotherapy, but option of radiotherapy to para-aortic and ipsilateral iliac lymph node is also valid.

6.4 Stage III and IV:

6.4.1 Chemotherapy.

6.5 If surgery performed by scrotal excision:

6.5.1 To irradiate scrotal scar with electron beam to a dose of 20-25 Gy including ipsilateral inguinal area. If patient wants to preserve function, scrotal irradiation can be deferred after explaining to the patient the chances of recurrence.

6.6 Chemotherapy failure (stage III / IV)

6.6.1 Palliative Radiotherapy.

6.6.2 Lung bath in case of lung metastases.

7. Radiotherapy Protocol:

7.1. External Beam: Planning Technique

7.1.1 Patient preparation

7.1.1.1 The day before simulation

- Patient should avoid eating large amount of fruits and vegetables, beans and dairy products

7.1.1.2 The evening before simulation

- Patient should take two table spoons of laxative. This will help in bowel movements.

7.1.1.3 The day of simulation

- Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products. If he/she have not had a bowel movement in the past 16 hours, then he/she should take another two table spoons of laxative.

7.1.1.4 One hour before simulation

- Patient should evacuate the bladder and drink 500 cc of water before simulation to make bladder full (at least 70%).
- Repeat this bladder filling process before each of daily radiation treatments.

7.1.2 Immobilization

Knee & Ankle support, Alfa cradle if available will improve immobilization.

7.1.3 Orientation, set-up, marking and reference points

7.1.3.1 Patients lie in the supine position.

7.1.3.2 A standardized bladder protocol is used for planning and treatment as mentioned earlier.

7.1.3.3 Patient aligned with 3 laser beams. Set 3 marks on the patient skin. The middle one in the midline over upper the border of L2 vertebra and two lateral marks.

7.1.3.4 Permanent ink (or tattoo) is applied to the lateral and midline reference points.

7.1.4 Image acquisition

- **Conventional Simulation**

It is used for Para aortic nodal radiotherapy or in patients where ipsilateral iliac or inguinal nodes are irradiated.

7.1.5 Target definition

7.1.5.1 For Para aortic lymph nodes

- Superior : lower border of T10
- Inferior : lower border of L5
- Lateral: to borders of transverse processes of vertebrae with inclusion of ipsilateral renal hilum.

7.1.5.2 For Para aortic, ipsilateral iliac & inguinal lymph nodes:

- A larger rectangular field ('dog leg') is defined and shielding added to protect the kidneys, bladder and bowel.

7.1.6 Technique

3D- Conformal radiotherapy.

7.1.7 Beam arrangement

PA/AP fields:

7.1.8 Beam Energy

10 – 15 Mv.

7.1.9 Dose prescription and fractionation

7.1.9.1 Seminoma Stage I

20 Gy in 10 daily fractions are given in 2 weeks.

7.1.9.2 Seminoma Stage IIA

30 Gy in 15 daily fractions given in 3 weeks.

7.1.9.3 Seminoma Stage IIB

36 Gy in 18 daily fractions given in 3½ weeks.

7.1.9.4 Stage III & IV **(**Chemotherapy failure**)**

7.1.9.5 Palliative Radiotherapy

- 20 Gy in 5 daily fractions given in 1 week.
- 30 Gy in 10 fractions given in 2 weeks

7.1.10 Dose limitation to Organs at risk

- Normal kidney as much as possible should be excluded from the field using shielding.
- Lead shields are used to protect the remaining testis from scattered irradiation and preserve fertility.
- Dose to OAR according to the QUANTEC recommendation.

7.1.11 Verification and plan execution

7.1.11.1 The treatment isocentre on a DRR from the CT simulation is compared with Portal images of the isocentre on the treatment machines using electronic portal imaging.

7.1.11.2 Off-line correction protocols are used for standard conformal treatment.

7.1.11.3 Images are taken on days 1 and weekly thereafter with a correction is made if the mean error in any one plane is ±5 mm.

7.2 Brachythrapy

Not Applicable

7.3 Sequelae of treatment

7.3.1 Nausea and vomiting are common side effects and can be reduced with prophylactic antiemetics.

7.3.2 If the patient has a history of peptic ulceration, a proton pump inhibitor should be prescribed with antiemetics.

7.3.3 The skin reaction is mild.

7.3.4 Dog leg fields and scrotal irradiation using testicular shielding, however, it gives some dose (0.7 Gy and 1.5 Gy respectively) and patients should be counselled accordingly.

7.3.5 They can be reassured that the para-aortic treatment does not result in any significant dose to the testis nor impaired fertility in the long term.

8. Principle of Hormonal Treatment

Not Applicable

9. Principle of Chemotherapy

- High risk, young Stage 1 patients desire to preserve fertility 1 cycle of single agent carboplatin can be considered**.**
- Kindly refer to medical oncology guidelines for chemotherapy**.**

10. Management of Recurrence/Relapse

Chemotherapy as per Medical Oncology Department Protocol

11. Follow Up

Weekly follow up during radiotherapy for assessment of toxicity after completion of treatment: Table (A. 5.a)

Period	Clinical Examination	Markers (βHCG/AFP)	CXR	CT scan
First year every 3 months.	Each visit	Each visit	Each visit	Yearly
Second year every 4 months.	Each visit	Every 6 months	6 months	Yearly
Third year every 6 months.	Each visit	Every 6 months	6 months	Yearly
Fourth year every 6 months.	Each visit	Every 6 months	6 months	Yearly
Fifth year yearly.	Each visit	Yearly	Yearly	Yearly

And to continue yearly follow up.

12. Ongoing Deparmental studies:

Not Applicable

13. References:

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A.6- RENAL CELL CARCINOMA CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

World wide the estimated new cases in 2012 was 213, 900. In US the estimated new cases in 2016 is 62.700. In gulf area, the ASIR from 1998- 2007 was 2.2 in males and 1.4 in females per 100,000. In Kuwaiti, in 2012 the ASIR was 4 and 2.1 for Kuwaiti male and female, and in non Kuwaiti, it was 2.2 and 0.5 4 respectivly.

2. Clinical Presentation:

2.1 A wide range of symptoms can be present with renal carcinoma depending on which areas of the body have been affected include:

2.2 The majority of renal tumors are asymptomatic and are detected incidentally on imaging, usually for an unrelated cause.

2.3 The classic triad is hematuria, flank pain and an abdominal mass. This triad only occurs in 10-15% of cases, and is generally indicative of more advanced disease.

3. Diagnostic Work up:

On suspecting of a renal cancer clinically initial work-up to reach diagnosis should include:

3.1 Complete history & General Physical Examination to assess the performance status.

3.2 Laboratory tests:

- 3.2.1 Full blood count, renal and liver function tests, corrected serum calcium, LDH and 24 hours urine protein.

3.3 Radiological tests:

- 3.3.1 CT scanning is used to assess the pelvis & abdomen with CT or MRI with or without contrast depending on renal insufficiency.
- 3.3.2 Chest imaging.
- 3.3.3 Bone scan or MRI brain if clinically indicated.
- 3.3.4 PET scan is considered on individualized basis
- 3.3.5 Consider needle biopsy if clinically indicated.

3.4 Histopathology assessment:

- 3.4.1 Tumor size
- 3.4.2 Histopathological type clear cell vs non clear cell.
- 3.4.3 Extension into veins or peri-nephric tissues
- 3.4.5 Extension into Gerota's fascia
- 3.4.6 Positive lymph nodes
- 3.4.7 Fuhrman grade
- 3.4.8 Margin status or extension into the vena cava or adjacent structure
- 3.4.9 Pathology review

4. Staging:

The TNM staging system should be used **AJCC staging system** 7th edition, (2010). After staging work up is finalized, the case is discussed in multidisciplinary genitourinary group including Radiation Oncologists, Onco-surgeons, & Medical Oncologists.

5. Prognostic Factors

5.1 Criteria:

5.1.1. KPS< 80.
5.1.2. HB< lower limit.
5.1.3. LDH> 1.5 limit.
5.1.4. Corrected serum Ca > 2.5 mmol/l.
5.1.5. Interval of less than a year from original diagnosis to the start of systemic therapy.
5.1.6. Two or more than 2 organ metastasis.

5.2 Categories:

5.2.1. Low risk: no risk factor
5.2.2. Intermediate risk: one or two risk factors
5.2.3. High risk: three, four, or five risk factors

6. Treatment

6.1 Surgery:

Surgery is the main treatment for most renal cell carcinomas. The chances of surviving a renal cell cancer without having surgery are small. Even patients whose disease has spread to other organs may benefit from surgery to take out the kidney tumor.

6.1.1 Radical Nephrectomy is performed in most of the cases.
6.1.2 Laparoscopic Nephrectomy has quickly become a preferred method for removing kidney tumors.
6.1.3 Partial Nephrectomy is also considered in selected cases.

6.2 Treatment by stage:

6.2.1 Stage IT1a:

6.2.1.1 Active surveillance in selected cases.
6.2.1.2 Partial nephrectomy (preferred) or radical nephrectomy if partial nephrectomy is not feasible or central location.

6.2.2 Stage I1b:

6.2.2.1 Partial nephrectomy.
6.2.2.2 Radical nephrectomy

6.2.3 Stage II, III:

6.2.3.1 Radical nephrectomy.

6.2.4 Stage IV:

6.2.4.1. Potentially surgically resectable solitary metastatic site: Nephrectomy and surgical metastatectomy.

6.2.4.2. Potentially surgically resectable primary with multiple metastatic sites: Cyto-reductive surgery before systemic therapy.

6.2.4.3. Medically or surgically un-resectable or relapse: Target therapy according to histopathology type or chemotherapy and risk assessment.

6.2.4.4. Best Supportive care can be considered in some patients with poor Performance status, multiple comorbidities, renal impairment.

7. Radiotherapy protocol:

Renal cell carcinomas are not very sensitive to radiation. Radiation therapy can be used to treat kidney cancer if a person's general health is too poor for them to have surgery. For patients who can have surgery, using radiation therapy before or after removing the cancer is not routinely recommended because studies have not shown any survival benefit. Radiation therapy is more often used to **palliate,** or ease, symptoms of kidney cancer such as pain, bleeding, or problems caused by cancer spread (especially to the bones, soft tissues masses or brain).

7.1 External Beam radiotherapy

7.1.1 Patient preparation: **According to the anatomical site.**

7.1.2 **Immobilization: According to the anatomical site.**

7.1.3 **Orientation, set-up, marking and reference points:** According to the anatomical site.

7.1.4 **Image acquisition:**

7.1.4.1 CT simulation

- CT examination is performed on a spiral CT scanner using a slice thickness of 3 mm.
- Slices range different according to the treated area
- An isocentre is tattooed in the CT scanner, as are lateral reference points.

7.1.4.2 X-ray Simulator

- If AP beams are to be used for palliation, the borders can be defined in the x-ray simulator.
- The beam centre is marked with a reference tattoo and the borders are drawn on the skin

7.1.5 Target definition: **According to the anatomical site to be treated.**

7.1.6 **The Technique:**
Three D-Conformal technique

7.1.7 **Beam arrangement:** AP/PA or multiple fields according to the anatomical site to be treated.

7.1.8 **Beam Energies:** 6-18 MV **according to the anatomical site to be treated.**

7.1.9 Dose prescription and fractionation :

7.1.9.1 20 Gy in 5 daily fractions given in 1 week.

7.1.9.2 30 Gy in 10 fractions given in 2 weeks.

7.1.10 Dose limitation to OAR: **according to the anatomical site to be treated and as per QUANTEC recommendation.**

7.1.11 Verification and plan excution:

7.1.11.1 Ideally the treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.

7.1.11.2 KV/MV portal images are taken for the first 3 days of treatment then weekly at least. These images to be approved by the treating oncologist before attempting subsequent treatment sessions.

7.1.11.3 A correction made if the mean error in any one plane is _5 mm

7.2 Brachytherapy:

Not applicable.

7.3 Sequleae of treatment:

It varies according to the treated anatomical site.

8. Principle of Hormonal therapy

Not Applicable

9. Principles of Chemotherapy/Target therapy

9.1 Several target therapy are available for clear cell histology as:

Sunitinib: 50 mg once a day PO for 4 weeks then 2 weeks rest

Other agents includes: ***Temsirolimus, Bevacizumab+ IFN, Pazopanib, Axitinib, Sorafinib***

9.2 For non clear cell RCC:

- Targeted Therapy: Sunitinib
- Chemotherapy: Gemcitabine, Capecitabine, or Doxorubicin (in sarcomatoid).

Kindly refer to medical oncology guidelines.

10. Management of recurrence/Relapse:

- ***Second line systemic therapy***
- Palliative Radiotherapy

11. Follow up

No single follow up plan is appropriate for all patients. Follow up should be individualized based on patient and tumor's characteristics. The usual practice is:

11.1 H & P every 3 months x 2 years.

11.2 4 monthly 3 rd year.

11.3 6 monthly 4th, and 5th year, then annually.

11.4 Metabolic bannel every 3 months for 2 years

11.5 CT after 6 months post op, then annualy.

12. Ongoing departmental studies

Not Applicable

13. References:

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GYNAECOLOGICAL MALIGNANCIES

A.7- CERVICAL CANCER CLINICAL MANAGEMENT GUIDELINES

1-Epidemiology:

Cervical cancer is the fourth most common cancer in women worldwide, and it has the fourth highest mortality rate among cancers in women. The global yearly incidence in 2012 was 528, 00 cases and the annual death rate was 266, 00. The estimated new cases and deaths from cervical cancer in the United States in 2015 are 12,900 and 4,100 respectively.

In gulf area, the ASIR in 2009 is 2.4 per 100,000. In Kuwait, in 2012 the overall ASR was 2.8 cases /100,000.

Squamous cell carcinoma accounts for approximately 80% of all cervical cancer and adenocarcinoma about 20 %.

2. Clinical Presentation:

2.1 Intraepithelial or early invasive carcinoma of the cervix can be detected before it becomes symptomatic by cytological smears; Papanicolaou (Pap) smear, colposcopy and biopsies, and HPV testing have high specificity and sensitivity (94.5%).

2.2 Frequently, the first manifestation of abnormality is post-coital spotting, which may increase to metrorrhagia (inter-menstrual bleeding) or more prominent menstrual bleeding (menorrhagia).

2.3 If chronic bleeding occurs, the patient may complain of fatigue or other symptoms related to anemia.

2.4 Serosanguinous or yellowish, foul-smelling vaginal discharge may be noted in patients with advanced invasive carcinoma.

2.5 Pain in the pelvis or hypogastrium may be caused by tumor necrosis or associated pelvic inflammatory disease.

2.6 In patients with pain in the lumbosacral area, the possibility of para-aortic lymph node involvement with extension into the lumbosacral roots or hydro nephrosis should be considered.

2.7 Urinary and rectal symptoms (hematuria, rectal bleeding) may appear in advanced stages as a consequence of invasion of the bladder or rectum by the neoplasm and may need specific evaluation of the urinary and gastrointestinal tracts.

2.8 The triad of sciatic pain, leg edema, and hydronephrosis is almost always associated with extension of disease into the pelvic side wall.

3. Diagnostic Work up:

3.1 Screening:

Based on solid evidence, screening via regular gynecologic examinations and cytological test (Papanicolaou [Pap] smear) with treatment of precancerous abnormalities decreases the incidence and mortality of cervical cancer. E**stimates from population studies suggest that**

screening may decrease cancer incidence and mortality by more than 80%. Screening is not beneficial in detecting invasive cancer in women younger than 21 years because of the low prevalence of invasive disease, in women older than 60 years if they have had a history of recent negative tests and it is less useful in diagnosis adenocarcinoma as it affects area that are hard to sample (endocervical canal).

ACS recommending screening for cervical cancer as follow:

3.1.1 Cervical cancer screening should begin at age 21 years. Women aged younger than 21 years should not be screened regardless of the age of sexual initiation or other risk factors.
3.1.2 For women aged 21 to 29 years, screening with cytology alone every 3 years is recommended. For women aged 21 to 29 years with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (ie, more than 3 years).
3.1.3 Women aged 30 to 65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable).
3.1.4 Women aged older than 65 years with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years, should not be screened for cervical cancer with any modality.

3.2 Clinical Assessment:

3.2.1 History &general Physical examination includes examination of the supraclavicular lymph nodes.
3.2.2 Pelvic examination: Thorough inspection of vulva, vagina and cervix.
3.2.3 Bimanual palpation of cervix to estimate tumor size, position, mobility and involvement of fornices or vaginal wall.
3.2.4 Parametrial invasion and extent assessed by per rectal exam.
3.2.5 Cervical biopsy for HP assessment if not taken.

3.3 Laboratory investigation:

3.3.1 CBC, LFT, KFT, and 24 hours creatinine clearance.
3.3.2 ConsiderHIV testing.Pregnancy test in premenopausal women.

3.4 Assessment of pathology

3.4.1 Histopathological assessment of the tumor type.
3.4.2 Slide review of the following points of biopsy or surgery at referral center:
3.4.2.1 Tumor size.
3.4.2.2 Grade.
3.4.2.3 Depth of invasion.
3.4.2.4 Horizontal spread.
3.4.2.5 Lympho-vascular space involvement (LVSI).
3.4.2.6 Cervical or parametrial invasion.
3.4.2.7 Lymph nodes invasion.

3.5 Radiological assessment:

3.5.1 CT of chest, abdomen and pelvis.
3.5.2 MRI of the pelvis.
3.5.3 PET/CT is optional.
3.5.4 Chest X-ray.
3.5.5 Bone scan if indicated.

3.6 Cystoscopy, urine cytology, and sigmoidoscopy can be considered for patients with suspected bladder or rectal invasion.
3.7 All patients are counseled for treatment options and toxicities.
3.8 After staging work up is finalized, the case is discussed in multidisciplinary group meeting.
3.9 Patient and family counseling for:
- 3.9.1 Physical and psychological health issues, including impact of treatment on quality of life, reproduction, risk of recurrence, and risk of second malignancies.
- 3.9.2 Smoking cessation for smokers. Attention to screening for colorectal

4. Staging TNM:

According to the American Joint Committee on Cancer (AJCC), 7th edition, 2010.

5. Prognostic factors:

The prognosis for patients with cervical cancer is markedly affected by the following factors:

5.1 Patient age and performance status.
5.2 Clinical stage: A multivariate analysis of prognostic variables in 626 patients with locally advanced disease (primarily stages II, III, and IV) studied by the GOG identified the following variables that were significant for progression-free interval and survival:

- 5.2.1 Periaortic and pelvic lymph node status. The status of the pelvic nodes was important only if the periaortic nodes were negative.
- 5.2.2 Tumor size, bilateral disease.
- 5.2.3 Pathological type: Approximately 25% of apparent squamous tumors have demonstrable mucin production and behave more aggressively than their pure squamous counterparts, suggesting that any adenomatous differentiation may confer a negative prognosis.

5.3 Delay in radiation delivery completion is associated with poorer progression-free survival.

5.4 Viral infection as Human immunodeficiency virus (HIV) HPV -18 DNA has been found to be associated with poor prognosis.

5.5 C-*myc* overexpression: associated with a poorer prognosis.

5.6 A polymorphism in the Gamma-glutamyl hydrolase enzyme, which is related to folate metabolism, has been shown to decrease response to cisplatin, and as a result is associated with poorer outcomes.

6. Treatment:

Treatment, of cervical cancer vary within each stage as the individual stages are currently defined by Féderation Internationale de Gynécologieet d'Obstétrique (FIGO).

6.1 Stage I A1:

6.1.1 If no LVI:

6.1.1.1 Core biopsy with negative margin (3mm) in those who want toretain the fertility.

6.1.1.2 If positive margin repeat cone biopsy or trachelectomy.

6.1.2 If + Ve LVI:

6.1.2.1 Core biopsy with negative margin (3mm) + PLND

6.1.2.2 Radical trachelectomy +PLND +/- PALN sampling.

6.1.2.3 Simple hysterectomy with or without oophorectomy.

6.1.2.4 Intracavitary brachytherapy – if unfit for surgery HDR: 7 Gy. / 5-6 Fr.

6.1.2.5 Radical hysterectomy + PLND in lympho-vascular invasion.

6.2 Stage IA2: (lymph node risk is 7.4%)

6.2.1 Radical hysterectomy with lymph node dissection is standard treatment.

6.2.2 Radical trachelectomy with pelvic lymphadenectomy (in patients who want to preserve fertility).

6.2.3 Radical radiotherapy if medically unfit. Point A dose 75 – 80 Gy.

6.2.4 If high risk pathological features, treat as IB.

***High risk pathological features include: Positive LN, positive surgical margin or positive parametrium.**

6.3 Stage IB1 and small volume stage IIA:

6.3.1 Radical hysterectomy with preservation of ovaries and lymphadenectomy+/PALN sampling.

6.3.2 Radical **trachelectomy** is an option for patient who wants to preserve fertility (limited to patients with tumors< 2 cm. diameter and no adverse prognostic factors).

6.3.3 Pelvic RT + Brachytherapy total point A dose 80-85 Gy+/- concurrent chemotherapy.

6.3.4 Radical RT if medically unfit or declines surgery. External pelvic RT: 45 Gy./25 Fr./5 weeks + Brachytherapy. Point A dose 80 – 85 Gy. HDR: 14 Gy./2 Fr.

6.3.5 Postoperative management according to surgical outcome: Post. operative External beam RT to pelvis to 50.4 Gy./28 Fr./5½ weeks and concomitant chemotherapy+/- vaginal brachytherapy in the following indication:

6.3.5.1. Absolute Indications:

6.3.5.1.1 Presence of tumor at resection margin.

6.3.5.1.2 More than one node positive.

6.3.5.1.3 Positive Parametrium.

6.3.5.2 Relative indications: (if more than one feature present)

6.3.5.2.1 Lympho-vascular invasion.

6.3.5.2.2 Deep stromal invasion.

6.3.5.2.3 Large primary tumors.
6.3.5.2.4 Poorly differentiated tumors.
6.3.5.2.5 Narrow resection margin (< 5 mm).
6.3.5.2.6 Single lymph node diameter > 4 cm.
6.3.5.2.7 Incidental finding at simple hysterectomy. Here, adjuvant pelvic RT only given.

6.3.5.3 Sedlis criteria for external pelvic radiotherapy post radical hysterectomy with node negative, margins negative and parametrium negative cases: Table.(A.7.a).

LVSI	Stromal invasion	Tumor size in cm Determined by clinical palpation
+	Deep 1/3	Any
+	Middle 1/3	≥ 2
+	Superficial 1/3	≥ 5
-	Middle or deep 1/3	≥ 4

LVSI: Lympho-vascular space invasion

6.4 Stage IB2 to (large volume) IIA2:

6.4.1 External pelvic RT + concurrent weekly Cisplatin.
6.4.2 Radiotherapy Dose: 45 to 50.4 Gy. in 1.80 Gy./ per Fraction + Brachytherapy: HDR: 7Gy x 3 Fr./ 3 weeks. Total Point A dose: ≥ 85 Gy.

6.5 Stage IIB:

6.5.1 Concurrent chemo-radiotherapy with Cisplatin.
6.5.2 EBRT to whole pelvis (WP) (45 – 50.4 Gy.) + Brachytherapy HDR: 7 Gy x 3 Fr./3 weeks and parametrial boost 10 Gy./5 Fr./1 week.

6.6 Stage IIIA:

6.6.1 Concurrent Chemo-Radiotherapy with Cisplatin.
6.6.2 EBRT to WP and whole vagina and medial inguinal lymph nodes to 45 – 50.4 Gy. + Brachytherapy.
6.6.3 Brachytherapy: HDR: 7 Gy.x3 Fr./3 weeks and parametrial boost if residual disease 10 Gy./5 Fr./1 week.

6.7 Stage IIIB - IVA:

6.7.1 Concurrent Chemo-Radiotherapy with Cisplatin.
6.7.2 EBRT to WP: 50.4 Gy./28 Fr./5½ weeks + Brachytherapy.
6.7.3 Brachytherapy: HDR: 7 Gy.x 3 Fr./ 3 weeks and parametrial boost 10 Gy./5 Fr./1 week.
6.7.4 If Para-aortic lymph node positive disease (FNAC proved).
6.7.4.1 If CT or PET /CT negative for distant **metastasis**:
Whole Pelvic RT + para-aortic lymph node RT, 45 – 50 Gy. to the CTV + concurrent Cisplatin containing CT+ Brachytherapy .
6.7.4.2 **If CT or PET /CT positive for distant metastasis:**
Consider biopsy of suspicious area.
6.7.4.2.1 If – ve treat as above.
6.7.4.2.2 If +ve for systemic chemotherapy and +/- individualized RT.

N.B: Grossly involved un-resected nodes can be boosted by 10-15 Gy/5-8f with careful attention of normal tissues around. Over all treatment time should not exceed 56 days.

6.8 Stage IVB:

6.8.1 Palliative treatment with Chemotherapy and / or Radiotherapy
6.8.2 Whole pelvis or para-aortic nodes.
6.8.3 20–30 Gy in 5–10 daily fractions given in 1–2 weeks.
6.8.4 8–10 Gy in 1 fraction for hemostasis.

7. Radiotherapy protocol:

7.1 External beam Radiation technique:

The following process is to provide current clinical treatment regimens for the radiotherapy of cervical cancer whether radical, post-operative, (with concomitant chemotherapy) or on palliative bases.

7.1.1 Patient preparation:

7.1.1.1 The day before simulation: Should empty rectum daily beforeradiotherapy.If constipated, should take laxative at night before RT planning and before RT treatment.
7.1.1.2 The day of simulation: Should drink 500ml of fluid 1hr before RT and not to micturate till after RT.
7.1.1.3 CT simulation: On day of simulation, patient taken to CT simulator for image acquisition.

7.1.2 Immobilization

7.1.2.1 Treated supine (unless grossly obese in which case treat Prone belly board if feasible.
7.1.2.2 Arms by side.
7.1.2.3 Knees supported by polystyrene wedge.
7.1.2.4 Ankle stocks.
7.1.2.5 No further immobilization.
7.1.2.6 Bladder comfortably full (1 to 2 hrs. post. Micturition).

7.1.3 Orientation, set-up, marking and reference points:

7.1.3.1 Patient is positioned by radiographers in Simulator.
7.1.3.2 Vaginal marker is placed at lower tumour extension and the introitus.
7.1.3.3 Patient aligned with 3 laser beams (anterior and 2 lateral). Set 3marks on the patient skin.
7.1.3.4 Reference marker then put anteriorly on top ofsymphysis pubis and lateral permanent ink (or tattoo) is applied to the lateral and midline reference points.

7.1.4 Image acquisition

7.1.4.1 **CT simulation: For radical treatment**

- CT examination will be performed on a four-detector spiral CT scanner. IV contrast may be given upon request of the referring radiation oncologist. CT cuts 5 mm.
- Distance takenfrom L4-5 interspace to below the obturator foramen or 3 cm below the lower extent of the tumor and should cover the vaginal markers.

7.1.4.2 Conventional simulator: For palliation and for haemostatic dose treatment volumes can be defined in the simulator. The patient lies supine with arms by their sides as lateral or oblique beams are not used. The GTV is defined from clinical extent of the disease and CT information.

7. 1.4.3 For patients who will be planned for PALN irradiation, CT is taken from T 9-10 interspace.

7.1.4.4 Images are transferred to the treatment planning system.

7.1.5 Target definition*:*

7.1.5.1 Whole Pelvis (radical):

7.1.5.1.1 The GTV: any macroscopic disease in the cervix plus any LN shown to be enlarged on imaging.

7.1.5.1.2 The CTV-T: Cervix CTV is the GTV plus the entire cervix and uterus, uterosacral ligament, the entire parametrium including ovaries, and upper half of vagina unless vaginal involvement then lower border to be 3cm below lowest extension. In extensive vaginal involvement, include the entire vagina.If uterosacral ligament involved include entire mesorectum. Care must be taken to not spare bowel at the extent of blocking the uterosacral ligament.

7.1.5.1.3 CTV-N: includes the pelvic lymph nodes, i.e. obturator, internal, external and common iliac and upper presacral 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.

7.1.5.1.4 The PTV: A typical CTV to PTV margin of 15–20 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.

7.1.5.1.5 Organ at Risk contouring:

- **Bladder:** will be outlined on every slice, including the portion inferior to the planning target volume. The contour includes the bladder contents.
- **Rectum:** will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid. The contour includes the rectum contents.
- **The femoral heads:** should be contoured in all slices.

7.1.5.2 In postoperative cases (adjuvant):

7.1.5.2.1 CTV: Vaginal vault and upper half of vagina or 3.5 cm vagina Inferior to vault which ever is greater. All are contoured on axial CT slices with the aid of the corresponding MRI.

7.1.5.2.2 Nodal CTV: is the common iliac, the external iliac to the Pelvic brim and the Internal iliac, obturator and upper presacral nodes. These aredelineated by identifying contrast-enhanced Pelvic blood vessels on each CT scan and using a 5 mm margin to create a 3D- CTV. If there is cervical stromal invasion the sub-aortic, presacral lymph nodes should be included. If there is disease in the lower third of the vagina the nodal CTV should include the lower presacral and the inguinal nodes.

7.1.5.2.3 PTV: Is drawn 1 cm isotropic ally around the CTV and to be expanded at the stump area to 1.2-1.5 cm.

7.1.5.3 Parametrium

- Anterior: Post wall of bladder or post border of external iliac.
- Posterior: Uterosacral ligaments and mesorectal fascia.
- Lateral: Medial edge int. obturator muscle / ischial ramus.
- Superior: Top of fallopian tube / broad ligament.
- Inferior: Urogenital diaphragm.

7.1.6 The Technique:

- **Three dimentional conformal radiotherapy is the standard techniques used in referral center.**
- Complex: IMRT techniques using five or seven photon beams may reduce dose to small bowel, rectum and bladder by shaping treatment to the pelvis. IMRT may also help to limit dose to pelvic bone marrow in patients undergoing chemoradiation. Organ motion studies have shown that the cervix and uterus position varies with both bladder and rectal filling by up to 20 mm. IGRT may be used to localise the target volume on a daily basis with a full IMRT implementation programme to ensure that it is delivered accurately and safely. Currently not available in referral center.

7.1.7 Beam arrangement:

The pelvis is usually treated with a four-field external beam arrangement +/- segmented fields. Care must be taken in designing the lateral fields so that the entire uterus is compassed and the utero-sacral ligaments, which attach at S1 and S2, are included. Additionally, the uterus is often anteverted and a tight anterior margin can block some of the uterus. For this reason, also treatment planning, CT scans are quite useful and more accurate than just relying on radiographs.

7.1.8 Beam energies:

It varies from 10 to 18 MV as per plan and patient' s separation.

7.1.9 Dose prescription and fractionation:

7.1.9.1 Adjuvant radiotherapy

50.4Gy/28 fractions /5 weeks to the pelvis +/- vault brachytherapy if indicated.

7.1.9.2 ***Radical Radiotherapy***

7.1.9.2.1 **Stage 1B1 and IIA1:** 45Gy/25 fr/5 weeks to pelvis + HDR brachytherapy 21Gy/3 fr/one fraction per week to HR-CTV.

7.1.9.2.2 Stage IB2 and IIA2 50.4Gy/28 fr/5 weeks to pelvis + HDR brachytherapy 21Gy/3fr/3 week to HR-CTV.

7.1.9.2.3 Stage IIB, III 50.4Gy/28fr/5 weeks to pelvis + HDR brachytherapy 21Gy/3fr/3 week days to HR- CTV + unilateral or bilateral PSW boost 6-10Gy/3-5 fr/3 days.

7.1.9.2.4 Stage IVA5 0.4Gy/28fr/5 weeks to pelvis (consider parallel opposed fields) +/- HDR brachytherapy 21Gy/3fr/3 week to point A or to HR-CTV + Unilateral/bilateral PSW or PM boost 5Gy/3fr/3 days.

7.1.9.2.5 Stage IVB individualized pelvic treatment depending on site of metastases. If pelvic nodes are positive on surgery or imaging a unilateral or bilateral PSW boost should be added 6Gy/3fr/3 days or 9Gy/5f/1 week. If para-aortic nodes are positive on surgery or imaging 50 Gy/25f/5 weeks para-aortic field a parallel-opposed, or P/A fieldmatched to pelvic field.

NB: The brachytherapy may be customized by dose and fractionation according to individual patient circumstances to give an equivalent BED or EQD2. If brachytherapy cannot be performed and interstitial brachytherapy is not available/ clinically appropriate a conformal CTplanned EBRT boost can be performed to a dose of 63-68Gy.

7.1.9.3 Palliative radiotherapy

Individualized radiotherapy according to the site, 20Gy/5 fractions/1 week to small field or 30 Gy/10 fractions/2 weeks to large fields.

7.1.10 Dose limitation to OAR: **As per Quantec recommendation:**

7.1.10.1 Bladder:

Whole bladder V80 <15%, V75 <25%,V70< 35%, V65 < 50%

7.1.10.2 Rectum:

V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%.

7.1.10.3 Femoral head: 45 Gy maximum dose, V30 < 50%.

7.1.10.4 **Small bowel** should be contoured in all slices. V45 Gy< 195cc.

7.1.10.5 Both kidneys

- For bilateral kidneys irradiation (if PALN is included): Mean dose to one kidneys < 18 Gy, V 28 < 20 %, V23 < 30%, V 20< 32%, V 12< 55 %.
- If mean dos to one kidney >18 Gy, V6 to remaining kidney < 30%.

7.1.11 Verification and plan execution:

7.1.11.1 The treatment isocenter on a DRR from the CT simulation is compared with portal images of the isocenter on the treatment machines using electronic portal imaging.

7.1.11.2 Off-line correction protocols are used for standard conformal treatment.

7.1.11.3 Images are taken on days 1–3 and weekly thereafter with a Correction made if the mean error in any one plane is _5 mm.

7.2 Brachytherapy:

7.2.1 Introduction: Brachytherapy allows delivery of a very high dose to the central tumour volume to obtain maximal local control without exceeding the tolerance of surrounding normal tissues. It is feasible because the normal uterus and vaginal vault are relatively radio-resistant and there is rapid fall-off of dose at a distance from the cervix, protecting the adjacent rectum, bladder and small bowel. Gynaecological brachytherapy can be delivered at low, medium or high dose rate, or with pulsed brachytherapy, which uses many, closely spaced radiation fractions or pulses to mimic continuous LDR treatment. Two techniques can be used in gynaecological cancer:

- Intracavitary brachytherapy
- Interstitial brachytherapy may be useful as a boost treatment in selected patients, particularly if extensive parametrial involvement, vagina is involved by tumor or stupm recurrence. Currently not available at referral center.

7.2.1.1 GEC-ESTRO recommendations for image-based 3D Brachytherapy:

This method relies on CT and/or MR imaging rather than 2D orthogonal radiographs.

7.2.1.2 Prerequisites:

- Imaging at the time of brachytherapy with applicator.
- Adaptation to the tumor volume and topography.
- Adaptation to path of tumor regression.
- Adaptation to the position of OAR.
- Volume based dose prescription, evaluation and reporting.

7.2.1.3 Applicators used in gynaecological brachytherapy:

7.2.1.3.1 A number of different applicators are available for use with an intact uterus.

7.2.1.3.2 A central intrauterine tube is used with a vaginal applicator, which can consist of a cylinder, ovoids or a ring.

7.2.1.3.3 Applicators have been developed that contain holes for interstitial needles, which may be used to produce better coverage of inner parametrial disease. Vaginal vault brachytherapy can be delivered using a vaginal cylindrical applicator or vaginal ovoids. Both are available in varying diameters/sizes.

7.2.1.3.4 Ovoids produce a better dose distribution if coverage of the parametrial soft tissues is required, whereas cylindrical applicators mainly treat the vaginal mucosa.

7.2.1.3.5 Doses are prescribed to 0.5 cm from the surface of the applicator.

7.2.1.4 Methods:

- Patient is assessed for suitability for brachytherapy after the completion of 30-40 Gy of EBRT.
- After appropriate consent for the procedure, patient is admitted in the ward for bowel preparation and anaesthesia clearance.Under general anaesthesia, patient is positioned in lithotomy, parts painted and draped.
- Bladder is evacuated.
- Pelvic examination (EUA) is done to assess the extent of disease at brachytherapy.
- Uterine cavity is measured with a sound. The cervical canal is dilated if needed and a centraluterine tube of appropriate length is inserted.
- The vaginal applicators (Ring) is thenpositioned and fixed to the tub
- Vaginal packing is used to distance OAR from the applicator and to prevent rotation of the applicators.
- Foleys catheter is inserted and 1cc of Visipaque dye with 4 cc of saline is instilled into the bladder and secured.
- The applicators can be furthersecured using labial sutures and bandaging.
- Position of the applicators are confirmed with 2D orthogonal fluoroscopic imaging.
- After recovery from anaesthesia, patient is taken for CT imaging.
- Bladder is evacuated and instilled with 100 cc saline and clamped.
- 3mm CT slices are taken from L4/5 to 5 cm below ischial tuberosity.
- Target volumes are defined as per GEC –ESTRO recommendation based on the clinical findings and MRI imaging at diagnosis and clinical findings at brachytherapy.

7.2.1.5 Target Volumes:

7.2.1.5.1 **GTV**: Gross tumour volume is the macroscopic-palpable and visible residual tumour at brachytherapy.

7.2.1.5.2 **HR-CTV**: High risk CTV includes the GTV (at bachytherapy) + whole Cervix + presumed extra cervical tumour extension at brachytherapy (Clinically palpable indurations and residual "grey zones" in T2W MRI (If MRI done).

7.2.1.5.3 **IR-CTV**: Intermediate risk clinical target volume: HR-CTV+ presumed adjacent significant microscopic disease 0.5-1 cm.

7.2.1.5.4 IR-CTV is confined by anatomical borders: bladder, rectum, Pelvic wall.

7.2.1.5.5 In limited disease: IR-CTV will be HR-CTV+ margin of 1 cm.

7.2.1.5.6 In extensive disease: IR-CTV will be the initial macroscopic tumor (GTV at diagnosis) and margins depend on the extent at diagnosis and regression after EBRT.

7.2.2. Contouring organ at risk

When evaluating doses to $2cm^3$ of the most irradiated OAR, organ contouring is recommended.

7.2.2.1 **Rectum and rectal wall**: From recto-sigmoid junction to ano-rectal junction.
7.2.2.2 **Bladder**: From bladder top to urethra-vesical junction.
7.2.2.3 **Sigmoid colon**: From recto-sigmoid junction to junction with the descending colon.
7.2.2.4 **Small bowel**: Loops in the vicinity of high dose region.
7.2.2.5 vaginal wall.
7.2.2.6 The target volumes after approval are sent to ARIA for planning.
7.2.2.7. Doses are prescribed to volumes rather than reference points.

7.2.2.8 The **GEC-ESTRO** group has recently published recommendations on target volume concepts and plan evaluation using DVHs. GTV, high risk (HR) CTV and intermediate risk (IR) CTV. The bladder, rectum, sigmoid colon and small bowel are defined as OAR. The total dose, including EBRT dose, should be isoequivalent to > or = 85–90 Gy in 2 Gy fractions to D90 of the HR CTV, and 60 Gy for the IR- CTV. Doses of 87 Gy to the HR CTV have been associated with improved local control compared with doses below 87 Gy. Doses for 2 mL of tissue volume (D2cc) for the OAR are calculated at 2 Gy per fraction. Isoequivalent doses of 80–90 Gy for the bladder and 70–75 Gy for the rectum and sigmoid colon are generally accepted.

After the plan is approved by Consultant, the patient is taken in for plan execution (in the presence of the treating doctor and physicist) with the same bladder protocol.Rectal probe is put in to check the dose at various points in the rectum. At completion of treatment, applicators are removed and patient is sent back to the ward for observation and discharged the same day. Similar sessions are carried out at weekly intervals so that the entire treatment (external and internal radiotherapy) are completed in 7-8 weeks time.

7.2.2.9 ***Brachytherapy Dose****:*

7.2.2.9.1 Full application: Cervix: 7 Gy(X3) to HRCTV.
7.2.2.9.2 As boost to external, the dose will be 5.5 Gy(x2) to to upper3 cm of vagina at 0.5 cm below the surface of applicator.
7.2.2.9.3 If brachy is the sole modality of treatment, dose will be 7 Gy (x3) to upper 3 cm of vagina at 0.5 cm depth from the surface of the applicator.

7.2.2.10 ***Dose Specification to the tumor and OAR***

7.2.2.10.1 Including brachytherapy, rectal doses should not exceed 60-65Gy at EQD2. The GEC ESTRO and ICRU guidelines should be used to guide limits for normal tissues and for reporting of dose to normal tissue during brachytherapy procedures. Three rectal reference points must be marked on the lateral radiograph film, 0.5cm posterior to the posterior vaginal wall. The kidneys may need to be contoured if a para-aortic strip is used and a pre-treatment isotope renal scan will need to be performed if significant amounts of renal tissue will be irradiated.

7.2.2.10.2 Dose-limiting small bowel tolerance is reflected in the recommended dose-fractionation. These OAR should be outlined on all slices for DVH assessment. A PRV may be added, but in the transverse plane compromise may be needed to maintain these dose limits to OAR.

7.2.2.10.3 ***Small bowel:*** V45 Gy< 195cc
7.2.2.10.4 **Rectum**: 2cc rectum < 4.1 Gy

7.2.2.10.5 Sigmoid: 2 cc sigmoid < 4.1 Gy
7.2.2.10. 6 **Bladder**: 2cc bladder < 5.9 Gy

7.3 Sequelae of treatment

All toxicities are assessed and scored according to RTOG/EORTC criteria

7.3.1 **Acute adverse effects**: Pruritus, loss of pubic hair, dry, moist desquamation, reddening and irritation of the skin in the irradiated field, nausea,colitis, cystitis, vaginitis, tiredness near the end of treatment, diarrhea, rectal irritation, urinary frequency and dysuria, and depression of blood counts or renal impairment with the use of Cisplatin.

7.3.2 **Late adverse effects:** Vaginal stenosis, uretheral stricture, (1-3%), vesico-vaginal or recto-vaginal fistula (less than 2%), intestinal obstruction or perforation (less than 5%), femoral neck fracture(less than 5%).

7.3.3 **HDR brachytherapy complications**: Uterine perforation (less than 3 %), vaginal laceration, DVT (less than 1 %).

8. Principle of Hormonal therapy:

Not applicable

9. Principle of Chemotherapy:

9.1 All patients will receive concurrent chemotherapy with weekly cisplatin 40 mg/m^2, maximum dose 70 mg intravenously during external beam radiation therapy for a total of 6 weeks (If adequate renal function and performance status).

9.2 Chemotherapy should commence during the first week of radiotherapy.

9.3 Antiemetics and other supportive medications should be given during radiation Cisplatin is one of highly ematogenic drug with delayed vomiting so Emend 150 mg IVI over 20-30 minutes can be used.

9.4 Dose Calculation: The dose will be calculated using actual body weight. The dose Will be recalculated if there is a weight change of >10% from baseline.

9.5 *Preparation*: Patients will receive pre- and post-hydration.

10. Management of Recurrence / Relapse:

Central pelvic recurrence after radical chemo-radiotherapy:

All cases are discussed in MDT genitourinary meeting.

10.1 Consider surgery, pelvic exenteration (anterior, posterior or total) with formation of one or two stomata (ileal conduit or colostomy).

10.2 Pelvic side wall recurrence palliative treatment. See Technical protocol for radiotherapy details.

10.3 Multiple sites or unresectable: chemotherapy or best supportive care.

10.4 For recurrence in the pelvis after initial radical surgery, radiation therapy and chemotherapy (fluorouracil with or without mitomycin) may cure 40% to 50% of patients.

10.5 Palliative chemotherapy: Drugs used for palliative chemotherapy are Cisplatin, Ifosfamide, Paclitaxel, Irinotecan, Bevacizumab, or combination chemotherapy.

10.6 Pelvic exenteration: No standard treatment is available for patients with recurrent cervical cancer that has spread beyond the confines of a radiation or surgical field. For locally recurrent disease, pelvic exenteration can lead to a 5-year survival rate of 32% to 62% in selected patients. These patients are appropriate candidates for clinical trials testing drug combinations or new anticancer agents.

N.B palliative chemotherapy is used for local or systemic relapse. Palliative radiotherapy is used when indicated.

11. Follow Up

11.1 H & P and PAP test:

11.1.1 every 3 months x 1 year.
11.1.2 every 4 months x 1 year
11.1.3 every 6 months x 3 years,
11.1.4 Then, annually.

11.2 CXR - annually.
11.3 CBC, KFT every 6 months.
11.4 CT /MRI/ PET as clinically indicated.
11.5 Cervical and vaginal cytology annually
11.6 Patient education regarding symptoms of recurrence, healthy life style, obesity, exercise and nutrition.
11.7 Patient education about sexual health and vaginal lubricant.

12. Ongoing Departmental studies:

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A.8- UTERINE CANCERS: CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

Uterine cancer is a common malignant lesion arising from the female genital tract.
In 2008, worldwide 2,88,000 women were diagnosed with uterine cancer with mortality rate1.7-2.4 /100,000 women. In US, the estimated new cases in 2016 is 60.05. The ASIR in GCC states is 2.9 per 100, 000 female. Incidence rate is about 4.2% in Kuwaiti women and 5.3% in non-kuwaiti women (Kuwait Cancer Registry, 2012). 75% of patients are postmenopausal. About 90% of cancers are typical endometrial adenocarcinomas.

2. Clinical Presentation:

2.1 Most common symptom is postmenopausal bleeding (75-90%).
2.2 A diagnosis of endometrial carcinoma may be considered in peri-menopausal women with heavy or prolonged bleeding, and in premenopausal women with abnormal bleeding patterns who are obese or oligo-ovulatory.
2.3 Sometimes it can be an incidental finding on imaging or at hysterectomy for benign causes.
2.4 Symptoms due to involvement of surrounding structures and due to metastases.

3. Diagnostic Work up:

3.1 SCREENING:

Based on the American Cancer Society Early detection Guidelines, those who have 22-50% lifetime risk of endometrial carcinoma like in patients with known

- HNPCC genetic mutation carrier status.
- Substantial likelihood of being a mutation carrier or
- Women from families with an autosomal dominant predisposition of colon cancer in the absence of genetic testing results.
- Recommendations are based on expert opinion:-annual testing for early cancer detection at age 35 years-endometrial biopsy.

3.2 History and physical examination:

3.2.1 Hysteroscopy – OPD procedure under LA. It allows inspection of uterine cavity.
3.2.2 Pipette biopsy- OPD procedure, involves taking samples of endometrium through long plastic tube.
3.2.3 EUA and curettage if patient cannot tolerate OPD procedure. Anaesthetic assessment especially in obese, hypertensive, diabetic or patients with heart disease.
3.2.4 Inspection of vulva, vagina, cervix, bi-mannual palpation.
3.2.5 Dilatation of cervix, with or without hysteroscopy.
3.2.6 Curettings from endocervical canal and uterine body.
3.2.7 Cystoscopy or sigmoidoscopy if extension to bladder or rectum is suspected.

3.3 Assessment of pathology:

3.3.1: Tumor size, site
3.3.2: Grade, histology
3.3.3: Depth of myometrial infiltration, cervical stromal involvement, adnexal and serosal involvement.
3.3.4: Pelvic and paraaortic LN assessment and involvement
3.3.5: Positive peritoneal fluid cytology
3.3.6: Assessment of hormone receptor status and molecular prognostic factors.

3.4 Labs:

3.4.1 Routine blood count
3.4.2 Biochemical profile.
3.4.3 Serum CA125 (may be useful for follow up).
3.4.5 Pregnancy test in premenopausal

3.5 Radiological evaluation:

3.5.1 TVUS - can detect a thickened endometrium. The endometrium is abnormal if it is greater than 4-5 mm in post-menopausal women who do not take hormone replacement therapy.
3.5.2 MRI of pelvis (MRI superior to TVUS or CT in detecting depth of myometrial invasion.
3.5.3 CT scan of chest and abdomen
3.5.4 Bone scan if clinically or biochemically indicated.

4. Staging TNM:

According to the American Joint Committee on Cancer (AJCC), 2010, **7th edition.**

5.Prognostic factors:

5.1 Host resistance factors:

5.1.1 Age
- Younger patient – Better outcome
{earlier, better differentiated tumors, little myometrial invasion}
- Older pts > 60yrs -atrophic uterus → tumor close to lymphatic rich serosa → LN mets

5.1.2 Poor PS
5.1.3 Anemia

5.2 Tumor Virulence Factors:

5.2.1 **Stage**: outcome less favorable with advancing stage: Table. (A.8.a)

STAGE	I	II	III	IV
5 YR Survival (%)	92	80	40	5

5.2.2 Tumor grade: affects the depth of myometrial infiltration and lymph node metastases.
5.2.3 Histology:

Worse prognosis regardless of grade
- Papillary Serous.
- Clear cell.
- Squamous & Undifferentiated types.
- Overall survival in this group <35%.

5.2.4 Depth of myometrial infiltration: consistently identified with treatment failures.

5.2.5 Lower uterine segment involvement, cervical stromal involvement, adnexal and serosal involvement along with capillary lymphovascular space involvement carries poor prognosis.

5.2.6 Pelvic and paraaortic lymph node involvement is a major predictor for distant disease.

5.2.7 Positive peritoneal fluid cytology carries increased risk of lymph node involvement but in the absence of other adverse prognostic factors- this is unlikely to act as an independent predictor for relapse.

5.2.8 Molecular prognostic factors:

- Ploidy-aneuploid tumors.
- HER -2 neu expression, poor outcome.
- P53 gene overexpression.

5.3 **Treatment related factors**:

- Delay in initiating adjuvant treatment.
- Surgery to RT interval > 6 weeks has adverse affect on the DFS and local control.

6. Treatment:

A total abdominal hysterectomy with bilateral salpingo-oophorectomy is the mainstay of treatment for all tumors of the corpus uteri. Histological staging and prognostic factors are determined from the surgical specimen and are used to guide adjuvant treatment.

6.1 Endometroid Histologies:

6.1.1 Operable:

- Standard primary treatment is:

Total hysterectomy + bilateral salpingo-oophrectomy (TAH / BSO), peritoneal cytology, pelvic and para-aortic lymph node dissection adjuvant radiotherapy according to risk group.

- Laparoscopic or vaginal hysterectomy is an option for patients unable to undergo abdominal procedure. eg. very obese.

6.1.2 Inoperable: for radical radiotherapy according to the stage.

- Post-operative Endometrial Cancer:

(Table.A.8.b) Treatment recommendations for post-operative radiotherapy of endometrial cancer.

FIGO Stage	Grade	Treatment Recommendation
IA (no GIC)	1,2 (not clear cell/ Papillary serous)	No further treatment But may discuss vault brachy if G2 with LVSI or near 50% invasion
IA with myometrial invasion (no GIC)	3 (no LVSI)	Vault brachy
IA or IB (GIC present)	1,2 (no LVSI)	
IA or IB (GIC present)	1,2 (LVSI)	EBRT with vault brachy boost
IA with myometrial invasion (no GIC)	3 (LVSI)	EBRT with vault brachy boost Consider PORTEC-3
IA or IB (GIC present)	3	
II	All grades	
IB-II	Clear cell or Papillary serous Histology	

III	All grades	EBRT with vault brachy boost Consider PORTEC-3 (not if vaginal invasion), Consider adjuvant chemo
Positive/ Suspicious Washings	1,2 (no LVSI),no Clear cell or Papillary serous	Patient to see clinical oncologist but low preference for chemo. No pelvic RT.
IV	All grades	Consider adjuvant chemo Consider EBRT if pelvic residual disease

GIC = Glandular Involvement of Cervix
Brachytherapy alone
21Gy/3#/2 weeks @ 0.5cm treating once a week
See RT Technical Protocol for radiotherapy details.

6.2 Papillary serous or clear cell carcinoma or carcinosarcoma.

6.2.1. Surgery as for ovarian epithelial cancer:

- TAH / BSO
- Pelvic and para-aortic lymph node dissection.
- Cytology
- Omentectomy.
- Biopsies of peritoneal surfaces (including under surface of diaphragm).
- Maximal tumor debulking.

6.2.2. Postoperative adjuvant treatment:

- Stage IA: External pelvic RT + Brachytherapy.
- Stage IB, IC, stage II and stage III & IV adequately debulked: chemotherapy +Tumor directed RT.
- Stage III and IV – inadequately debulked: chemotherapy.

6.3 Uterine Sarcoma (LMS and ESS)

Adjuvant treatment for high grade tumors after initial surgery as for Endometrial Cancer.

6.3.1 Stages 1.2 and 3 with no residual disease. 45 Gy./25 Fr./5 weeks to true pelvis + Vaginal brachytherapy (as before for Endometrial cancer).

6.3.2 Stage 3 with residual disease: 45 Gy./25 Fr./5 weeks to true pelvis + small vol. RT to residual disease 14.4 – 19.8 Gy./ 8-11 Fr. / 2 weeks.

6.3.3 Stage 4: referred to medical oncology for chemotherapy.

7. Radiotherapy Protocol:

The following process is to provide current clinical treatment regimens for the radiotherapy of endometrial cancer in the context of post-surgery adjuvant treatment, radical radiotherapy in inoperable cases and on palliative bases

7.1 External Beam: Planning Technique

7.1.1 Patient preparation:

7.1.1.1 The day before simulation:

If constipated, should take laxative at night 3 days before RT planning

7.1.1.2 The day of simulation:

Rectum should be empty

All patients should drink 500 ml of fluid 1/2 hr before planning CT to ensure adequate bladder filling.

7.1.2 Immobilization:

- Patients undergoing conformal radiotherapy are planned and treated lying supine (unless grossly obese in which case treat prone with belly board if feasible), arms by side.
- Knees supported by polystyrene wedge.
- Ankle stocks.
- No further immobilization.

7.1.3 Orientation, set-up, marking and reference points:

Patient is positioned by radiographers in CT Simulator.

- Vaginal marker is placed in the patient at introitus.
- Aligned with anterior and lateral lasers.
- Reference marker then put anteriorly on top of symphysis pubic and lateral
- laser points marked

7.1.4 Image acquisition:

7.1.4.1 CT simulation

- CT cuts 5 mm distance taken from L3-4 interspace to 4 cm below obturator foramen.
- Acquired images after confirming with the Radiation Oncologist is transferred to the treatment planning system.

7.1.4.2 Simulator: For palliation and for haemostatic dose treatment volumes can be defined in the simulator. The patient lies supine with arms by their sides as lateral or oblique beams are not used. The GTV is defined from clinical extent of the disease and CT information.

7.1.5 Target definition:

7.1.5.1 Adjuvant Radiotherapy:

7.1.5.1.1 There is no GTV postoperatively and CTV-T includes the vaginal vault and parametrial tissues.

7.1.5.1.2 CTV-N: includes the obturator, external and internal iliac Nodes and additional common iliac lymph nodes when indicated.

7.1.5.1.3. CTV-T and –N: are delineated using preoperative CT and MRI, operative diagrams and histological findings to include sites at high risk of recurrence. Guidelines have been proposed for standardised nodal CTV definition using CT scans with contrast-enhanced pelvic blood vessels (surrogate for lymph nodes) with a 7 mm margin.

7.1.5.1.4 A typical CTV-PTV margin of 10–15 mm is added for CTV-T and 7 mm for CTV-N to allow for organ motion and set-up errors, and is individualised depending on known results of departmental set-up variations.

Detailed CTV as per table. (A.8.c).

Detailed CTV (table A.8.c)

Target site:

Common iliac lymph nodes	From 7mm below the L4/L5 interspace to the level of the bifurcation of the common iliac arteries into the external and internal iliac arteries.
External iliac lymph nodes	From the level of the bifurcation of the common iliac artery into the external artery to the level of the superior aspect of the femoral head where it becomes the femoral artery.
Internal iliac lymph nodes	From the level of the bifurcation of the common iliac artery into the internal artery, along its branches (obturator, hypogastric) terminating in the paravaginal tissues at the level of the vaginal cuff.
Upper vagina	Vaginal cuff and 3 cm of vagina inferior to the cuff.
Parametrial/Paravaginal tissue	From the vaginal cuff to the medial edge of the internal obturator muscle/ischial ramus on each side.
Presacral lymph nodes[*]	Lymph node region anterior to S1and S2 region.

[*]**If patient has endometrial cancer with cervical stromal invasion**

7.1.5.2 ***OAR CONTOURING:***

- **Bladder**: will be outlined on every slice, including the portion inferior to the planning target volume. The contour includes the bladder contents.
- **Rectum**: will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid. The contour includes the rectum contents.
- **The femoral heads:** should be contoured in all slices.

7.1.5.3 **Primary radical radiotherapy:**

Non-surgical patients with stage I and II disease may have multiple co morbidities which limit the volume that can be treated radically. The GTV for uterine tumours is defined on clinical examination and with MRI. The CTV-T includes the whole uterus, cervix, ovaries, parametrium and upper half of vagina. Involved nodes are detected by CT or MRI. If the whole vagina is involved, the inguinal nodes may need to be included in the CTV-N. A CTV-PTV margin of 10–15 mm is commonly used to allow for set-up uncertainty and physiological movement of the corpus and bladder.

7.1.6 The technique:

Three dimnetional conformal radiotherapy

7.1.7 Beam arrangement

7.1.7.1 Conformal: With 3D target volume localisation, 3D dose planning can be used with individual shaping of each beam using MLC or shielding blocks

to spare normal tissues. One anterior, two lateral opposing and one partially weighted posterior beam are commonly used Conformal radiotherapy and systematic target volume definition significantly reduces dose to the rectum and bladder compared with conventional solutions, as well as avoiding geographical miss.

7.1.6.2 Conventional:

7.1.6.2.1 Pelvic Portal (AP-PA)

- Superior border: A transverse line between L4-L5.
- Lateral border: 1-2 cm lateral to the widest true pelvic diameter.
- Inferior border: A transverse line below the obturator foramen and at least 4 cm beyond the vaginal cuff. A radio-opaque marker in the vagina to mark the vaginal cuff will help to facilitate proper placement of the lower border.
- MLC blocking to shield small bowel and femoral heads should maintain a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina.

7.1.6.2.2 Pelvic Portal (lateral fields)

- Superior border: Identical to AP/PA fields.
- Anterior border: A line drawn through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4/L5
- Posterior border: Care should be taken to include at S3-S4.
- Inferior border: Identical to AP/PA fields.
- MLC blocking should be used to shield anterior small bowel if possible, maintaining a margin of at least 1 cm from common and external iliac nodes. Blocking may split the L4/L5 vertebral body to shield posterior soft tissue and split the sacrum to provide adequate margin for pre-sacral nodes. Posterior rectum may be blocked.
- When target volume for nodes and central CTV is contoured fields are defined accordingly.
- Generally beam arrangement is four field box techniques as above.

7.1.6.2.3 Para-Aortic Fields when indicated

- The GTV= Macroscopic lymph nodes
- The CTV= Lymph nodes from L5 up to T11dependant on involved nodes.
- The PTV= CTV+1cm
- Field Borders for Virtual Simulation
  - Superior: T12/L1
  - Inferior: Match to pelvic field
  - Lateral: Up to 8cm wide to cover nodes

7.1.6.3 Complex:

Pelvic IMRT has been shown to reduce the dose to bladder, rectum and small bowel by 20–50 per cent. This is especially important in the postoperative situation, with reducstion in acute and late morbidity. It may help to limit dose to pelvic bone marrow in patients undergoing chemoradiation.

7.1.8 Beam energies:

It varies from 10 to 18 MV

7.1.9 Dose prescription and fractionation:

7.1.9.1 Adjuvant radiotherapy

7.1.9.1.1 External beam irradiation

45–50.4 Gy in 25–28 daily fractions of 1.8 Gy given in 5–5½ weeks.

7.1.9.1.2 Vaginal vault brachytherapy as boost after EBRT for patients with cervical involvement HDR

- 5.5 Gy in 2 fractions at 0.5 cm from the surface of the applicator given at least a week apart.

7.1.9.1.3 Vaginal vault brachytherapy as sole adjuvant treatment for selected intermediate risk patients. HDR

- Total dose 21 Gy in 3 fractions, 7Gy/ fraction at 0.5 cm from the surface of the applicator given at least week apart between each application.

7.1.9.2 Primary radiotherapy

7.1. 9.2.1 Unoperated stage I, II and III disease

7.1.9.2.1.1 EBRT

50.4 Gy in 28 daily fractions of 1.8 Gy given in 5 weeks followed by intracavitary irradiation

7.1.9.2.1.2 Intracavitary irradiation

HDR 5.5Gy in 2 fractions.

7.1.9.2.1.3 EBRT boost

Rarely, if intracavitary treatment is not feasible EBRT may be followed by an additional dose to the GTV using a conformal plan.
Dose: 15–20 Gy in 8–11 daily fractions of 1.8 Gy given in 1½–2 weeks.

7.1.9.2.2 Intracavitary radiotherapy alone for primary disease, if unfit for EBRT

HDR

- 21 Gy in 3 fractions

7.1.9.2.3 Para-aortic radiotherapy

- 45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.

7.1.9.3 Palliative radiotherapy:

- 20 Gy in 5 fractions given in 1 week.
- 30 Gy in 10 fractions given in 2 weeks.
- 8–10 Gy as a single fraction for haemostasis.

7.1.10 Dose limitation to OAR:

According to Quantec normal tissues tolerance recommendation

7.1.10.1 Small bowel:

- V45 Gy < 195cc

7.1.10.2 Kidneys:

For bilateral kidneys irradiation

- Mean dose to one kidneys < 18 Gy, V 28 < 20 %, V23 < 30%, V 20< 32%, V 12< 55 %,
- If mean dos to one kidney >18 Gy, V6 to remaining kidney < 30%

7.1.10.3 Rectum:

V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%

7.1.10.4 Bladder:

Whole bladder V80 <15%, V75 <25%, V70 < 35%, V65 < 50%

7.1.11 Verification and plan execution:

7.1.11.1 The treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.

7.1.11.2 Off-line correction protocols are used for standard conformal treatment.

7.1.11.3 Images are taken on days 1–3 and weekly thereafter with a correction made if The mean error in any one plane is _5 mm.

7.2 Brachytherapy:

7.2.1 Introduction:

Brachytherapy allows delivery of a very high dose to the central tumour volume to obtain maximal local control without exceeding the tolerance of surrounding normal tissues. It is feasible because the normal uterus and vaginal vault are relatively radio-resistant and there is rapid fall-off of dose at a distance from the cervix, protecting the adjacent rectum, bladder and small bowel. Gynaecological brachytherapy can be delivered at low, medium or high dose rate, or with pulsed brachytherapy, which uses many, closely spaced radiation fractions or pulses to mimic continuous LDR treatment.

7.2.2 Methods:

7.2.2.1 Vaginal vault brachytherapy:

- Vaginal vault brachytherapy can be delivered using a vaginal cylindrical applicator or vaginal ovoids. Both are available in varying diameters /sizes.

- Ovoids produce a better dose distribution if coverage of the parametrial soft tissues is required, whereas cylindrical applicators mainly treat the vaginal mucosa.

- Doses are prescribed to 0.5 cm from the surface of the applicator.

7.2.2.2 Dose specification to the tumour and OAR

- As boost to external, the dose will be 5.5 Gy (x2) to upper 3 cm of vagina at 0.5 cm below the surface of applicator.
- If brachytherapy is the sole modality of treatment, dose will be 7 Gy (x3) to upper3 cm of vagina at 0.5 cm depth from the surface of the pplicator.

- Isoequivalent doses of 80–90 Gy for the bladder and 70–75 Gy for the rectum and sigmoid colon are generally accepted.

7.3 Sequelae of treatment

All toxicity are asses and scored according to RTOG/EORTC criteria

7.3.1 Acute adverse effects : Pruritis, loss of pubic hair, dry, moist desquamation, reddening and irritation of the skin in the irradiated field, nausea,,colitis, cystitis, vaginitis, tiredness near the end of treatment, diarrhoea, rectal irritation, urinary frequency and dysuria, and depression of blood counts or renal impairment with the use of Cisplatin.

7.3.2 **Late adverse effects:** Vaginal stenosis, urethral stricture, (1-3%), vesicovaginal or rectovaginal fistula (less than 2%), intestinal obstruction or perforation (less than 5%), femoral neck fracture(less than 5%).

HDR brachytherapy complications: vaginal laceration, DVT (less than 1 %)

8. Principle of Hormonal treatment:

Role of hormonal therapy in recurrent or metastatic disease has been evaluated only in endometroid histologies. Hormonal therapy is also used for selected patients with ESS. Progestational agents are mainly used in patients with metastatic disease, however tamoxifen with alternating megesterol may be used. Aromatase inhibitors are also being used. No particular drug, dosage or scheduling has been found to be superior. The main predictors of response in metastatic disease are well differentiated tumors, long disease free interval, expression of ER/PR rceptors, location and extent of extrapelvic metastasis.
Dose: Megestrol acetate (Megace): 160 mg daily.

9. Principles of Chemotherapy:

All cases are discussed in MDT meeting.

- Multiagent chemotherapy is preferred over single agent chemo in metastatic, recurrent and high risk disease.
- Carboplatin and paclitaxel based regimens are increasingly used with response rates of 40-62% and overall survival of 13- 29 months.

10. Management of recurrence /relapse:

Localized recurrence: pelvis or para-aortic lymph node or selective metastatic site.

10.1 Palliative R.T.
10.2 Progestational agents.
10.3 Chemotherapy
10.4 Consider clinical trials.

11. Follow Up

11.1 First follow up after 4 – 6 weeks.
11.2 H & P every 3 months x 1 year. ; 4 monthly – 2nd year. ; 6 monthly – 3rd, 4th, and 5th year, then annually.
11.3 CA.125 6 monthly (category 3 evidence).
11.4 CXR annually.
11.5 Vaginal cytology every 6 months x 2 yrs., then, annually.
11.6 Patient's education regarding symptoms.

12 Ongoing Departmental studies

12.1 Results of HDR vault brachytherapy in post operative cancer endometrium, Referral center experience.

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A.9- VAGINAL CANCER CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

Vaginal cancer is rare and comprising about 1 % of female genital cancer. Squamous cell carcinoma account 85 % of vagina cancer. In GCC the ASIR was 0.1 case per 100,000 cases from 1998-2007. The ASIR is 0% in Kuwaiti and non Kuwaiti women (reported as per Kuwait Cancer registry, 2012). Approximately 70% of primary vaginal malignancies are detected in women 60 years of age or older.

2. Clinical Presentation:

2.1 In 10% to 20% of the patients no symptoms are reported, and the diagnosis is made by cytological examination.

2.2 In patients with invasive disease, irregular vaginal bleeding, often postcoital, is the most common presenting symptom followed by vaginal discharge and dysuria.

2.3 Pelvic pain is a relatively late symptom, generally related to tumour extent beyond the vagina.

2.4 Primary vaginal squamous cell carcinoma arising from the posterior vaginal wall can present as a cystic pelvic mass resembling an ovarian neoplasm.

3. Diagnostic Work up

3.1 History and Physical Examination includes

3.1.1 Gynecologic history.

3.1.2 Prior surgical history

3.1.3 Prior radiation treatment or contra indications to radiation treatment.

3.1.4 Examination under anesthesia (EUA) if necessary to assess primary tumor volume and extent.

3.2 Assessment of pathology

3.2.1 Histologic diagnosis of vaginal cancer.

3.2.2 Review of pathology from other institutions.

3.2.3 Tumor size,location, grade of the tumor and molecular profile of the tumour

3.3 Laboratory investigations:

CBC, electrolytes, creatinine, liver function studies.

3.4 Radiological investigations:

3.4.1 Chest x-ray or CT chest (if clinically indicated).

3.2.4 CT abdomen and pelvis (if clinically indicated).

3.4.3 MRI pelvis.

3.4.4 PET/CT scan can be considered

4. Staging (TNM):

According to the American Joint Committee on Cancer 7 Th edition, (AJCC, 2010).

5. Prognostic factors:

5.1 The **stage** of disease is the most significant prognostic factor regarding ultimate outcome. The 10-year actuarial disease-free survival (DFS) is 94% for stage 0, 75% for stage I, 55% for stage IIA, 43% for stage IIB, 32% for stage III, and 0% for those with stage IV.

5.2 The prognostic importance of **lesion size** has been controversial, lesions measuring <5 cm in maximum diameter had a 20% 10-year local recurrence rate, compared to 40% for those lesions larger than 5 cm.

5.3 The impact of **lesion location:** better survival and decreased recurrence rates for patients with cancers involving the proximal half of the vagina when compared with those in the distal half, or those involving the entire length of the vagina.

5.4 **Histological grade:** is an independent, significant predictor of survival with a higher incidence of local recurrence in patients with adenocarcinoma compared with squamous cell carcinoma (52% and 20%, respectively, at 10 years), as well as a higher incidence of distant metastases (48% and 10%, respectively), and lower 10-year survival rate (20% vs. 50%). Other histologies as melanoma or sarcoma has a higher propensity for development of distant metastases.

5.5 Overexpression of HER-2/neu oncogenes in squamous cancer of the lower genital tract is a rare event that may be associated with aggressive biologic behaviour and a more favourable prognosis in gynaecologic tumours with an overexpression of wild-type p53 protein than in tumours containing mutated p53 genes.

5.6 Age: 5-year survival is 63.2% for patients below the age of 60, compared with 25% for those over 60 years of age ($p < 0.001$).

6. Treatment:

6.1 Stage I:

In patients with stage I lesions, usually 0.5- to 1-cm thick, that may involve one or more vaginal walls, it is important to individualize radiation therapy techniques to obtain optimal functional results. Brachytherapy alone is adequate for superficial stage I patients, with 95% to 100% local control rates. EBRT is advisable in patients with deeply infiltrating or poorly differentiated stage I lesions.

6.2 Stage II:

Patients with stage IIA (tumors have more advanced paravaginal disease without extensive parametrial infiltration) and 2B (with more extensive parametrial infiltration) are uniformly treated with EBRT, followed by ICB.

6.3 Stage III& IVa:

Use of concurrent chemo-RT with weekly cisplatin in advanced carcinoma vagina is an extrapolation of its noted benefit in improving the locoregional control, overall survival and disease free survival in locally advanced carcinoma cervix and vulva.

6.4 Stage IVb:

No established anticancer drugs can be considered of proven clinical benefit, although patients are often treated with regimens used to treat cervical cancer. Radiation can be used for palliation of symptoms with or without chemotherapy.

7. Radiotherapy Protocol:

The following process is to provide current treatment guidelines for the radiotherapy of vaginal carcinoma with aim of preventing locoregional recurrence. Adjuvant radiotherapy should be considered if surgical margins are close or positive. Pelvic exenteration with vaginal reconstruction is sometimes chosen for more advanced stages, residual or recurrent disease. Surgery is the treatment of choice if a vesicovaginal or recto-vaginal fistula is present at diagnosis. Ovarian transposition before radiotherapy can help to preserve ovarian function in the premenopausal patient.

7.1. External Beam: Planning Technique

***7.1.1 Patient preparation:* As in cervical carcinoma**

7.1.2 Immobilization: As in cervical carcinoma

No further immobilization

***7.1.3 Orientation, set-up, marking and reference points:* As in cervical carcinoma**

Additional points to note: The distal margin of the tumor should be identified with a radiopaque marker or bead at the time of the CT simulation.

7.1.4 Image acquisition

7.1.4.1 CT simulation

As in cervical carcinoma

7.1.4.2 Conventional Simulator

For palliation and for haemostatic dose treatment volumes can be defined in the simulator. The patient lies supine with arms by their sides as lateral or oblique beams are not used. The GTV is defined from clinical extent of the disease and CT information.

7.1.5 Target definition:

7.1.5.1 Target definition for EBRT:

7.1.5.2 GTV-T is the primary vaginal tumour as defined by clinical examination, EUA, and co-registered MRI or CT scans.

7.1.5.3 CTV-T includes the entire vagina, cervix and surrounding paravaginal tissues.

7.1.5.4 PTV-T is CTV-T+10-15mm margin

7.1.5.5 For tumours of the lower third, the introitus is also included.

7.1.5.6 CTV-N includes different pelvic lymph nodes below the common iliac nodes depending on the site of the primary tumour and is delineated with 7 mm margin around the pelvic blood vessels.

7.1.5.6.1 for tumours of the upper two-thirds of the vagina – obturator, external and internal iliac, presacral and para- rectal lymph nodes.

7.1.5.6.2 for tumours of the lower third of vagina – inguino-femoral and distal external iliac nodes.

7.1.5.6.3 for tumors involving the posterior vaginal wall – presacral and para-rectal deep pelvic nodes.

7.1.5.7 PTV-N: is CTV-N+ 5mm margin.

7.1.5.8 Palliative radiotherapy:

For palliation of locally advanced fixed and fungating vaginal tumors, either EBRT or, when technically feasible, brachytherapy can be given. Radiotherapy is limited to the GTV with a 15 mm CTV margin to reduce toxicity using a conformal plan where possible or CT- simulated opposing beams.

7.1.5.9 OAR contouring: refer to cervical cancer protocol.

7.1.6 TECHNIQUE:

Three dimentional conformal radiotherapy

7.1.7 Beam arrangement:

7.1.7.1 Planned conformal fields to treat the primary tumour, depending on the extent and location of local disease and the need to treat the nguinal and deep pelvic lymph nodes.

7.1.7.2 AP-PA fields with differential weighting or conformal planning to treat inguinal and deep pelvic lymph nodes.

7.1.8 Beam energies:

6-18 MV +/- electron if indicated

7.1.9 Dose prescription and fractionation:

7.1.9.1 Primary tumour and lymph nodes: 45–50.4 Gy in 25–28 daily fractions of 1.8 Gy given in 5– 5½ weeks.

7.1.9.2 External beam boost if brachytherapy not feasible: 15–20 Gy in 8–11 daily fractions of 1.8 Gy given in 1½–2 weeks.As in cancer cervix.

7.1.9.3 ICB: 7 Gy x3 to 0.5 cm below the whole vaginal mucosa using Appropriate size vaginal cylinders.

7.1.9.4 In patients with tumours involving the middle and lower vagina with clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated electively to 45 to 50 Gy.

7.1.9.5 For patients with positive pelvic nodes or those patients with advanced disease, additional boost to the areas of gross disease, as defined by CT scan, should be given using conformal therapy to deliver a total dose between 65 to 70 Gy, when feasible, with high-energy photons.

7.1.9.6 Boost to the gross pelvic nodes after brachytherapy should be given using small fields (similar to the parametrial boost with

midline shielding) to deliver a total dose between 60 to 65 Gy with high-energy photons.

7.1.10 Dose limitation to OAR

Refer to the cervix protocol.

7.1.11 Verification and plan execution:

Refer to cervix protocol

7.2 Brachytherapy: when applicable

7.2.1 Cylindrical vaginal applicators can be used to deliver intracavitary Brachytherapy for VAIN or superficial tumors that are less than 5 mm deep, either at diagnosis or after EBRT. Where tumors are more than 5 mm deep, either at diagnosis or after EBRT, interstitial brachytherapy is required.

7.2.2 Interstitial implants using the Paris system. Currently not available in referral center.

7.2.3 Brachytherapy for tumors of the upper third of the vagina is delivered with the same technique as for cervical carcinomas, with a central intrauterine tube and vaginal applicators. A brachytherapy boost to tumors of the middle and lower third of the vagina, limited to the posterior wall, can be delivered using cylindrical applicators in both the vagina and rectum.

7.2.3 Target delineation for brachytherapy:

7.2.3.1 CTV-T _ GTV-T _ 2 cm margin.

7.2.3.2 After EBRT, brachytherapy is used to deliver a further localised high dose boost to residual GTV for stage I and II disease.

7.2.3.3 When volume of residual tumour precludes brachytherapy (e.g. stage III disease), repeat imaging is used to define a new GTV- T. Further EBRT is given using a conformal plan with a 15– 20mm margin for the CTV-T and a further 10 mm margin for the PTV.

7.3. Sequelae of treatment

Refer to cervix protocol

7.3.1 Acute adverse effects:

- Epilation of pubic hair, hyperpigmentation, and moist desquamation by 3rd – 5th week.
- Infection as: Candida, diarrhea, cystitis,
- Rectovaginal fistulas, vesicovaginal fistulas, rectal or vaginal strictures, and proctitis. Premature menopause from ovarian damage and soft tissue or bone necrosis.

7.3.2 Chronic adverse effect:

Atrophy of skin, telangiectasia, vaginal shortening, dryness, femoral neck fracture < 5%

8. Principles of hormonal treatment:

Not applicable

9. Principles of chemotherapy:

Concurrent chemotherapy using 5-fluorouracil or Cisplatin-based therapy and radiation is sometimes advocated. Cisplatin is used as in cancer cervix.

10. Management of Recurrence / Relapse

10.1 Recurrence carries a grave prognosis. In a large series, only five of fifty patients with recurrence were salvaged by surgery or radiation therapy. All five of these salvaged patients originally presented with stage I or II disease and had tumor recurrence in the central pelvis. Most recurrences occur in the first 2 years after treatment. In centrally recurrent vaginal cancers, some patients may be candidates for pelvic exenterating or radiation therapy.

10.2 No established anticancer drugs can be considered of proven clinical benefit, although patients are often treated with regimens used to treat cervical cancer. If eligible, patients should be offered the option of participation in one of the ongoing clinical trials.

11. Follow Up

As is the case with other gynecologic malignancies, the evidence base for surveillance after initial management of vaginal cancer is weak because of a lack of randomized, or even prospective, clinical studies. There is no reliable evidence that routine cytologic or imaging procedures in patients improve health outcomes beyond what is achieved by careful physical examination and assessment of new symptoms. Therefore, outside the investigational setting, imaging procedures may be reserved for patients in whom physical examination or symptoms raise clinical suspicion of a recurrence or progression.

12. Ongoing Departmental studies:

Not Applicable

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A.10- CARCINOMA OF VULVA: CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

It accounts for 3-5% of all female genital tract malignancies. Median age is 65-70 years. World wide incidence, the number of new cases of vulvar cancer was 2.4 per 100,000 women per year. The number of deaths was 0.5 per 100,000 women per year (SEER data). In GCC, the ASIR from 1998-2007 was 0.2. Similar rates of 0.2% in non Kuwaiti females and 0.3% in Kuwaiti females

2. Clinical Presentation:

2.1 Common symptoms are pruritus (90%), spotting or bleeding, pain, and discharge.

2.2 Depending on the extent and the location of the tumor, patients may also complain of dysuria, difficulty with defecation, and may also report difficulty or discomfort with intercourse.

2.3 Rarely, patients present with very advanced nodal disease or with edema of the lower extremities secondary to disease in the groins.

3. Diagnostic Work up:

3.1 History and Physical Examination includes

- Gynecologic history, prior surgical history (including local excision, laser treatment) prior radiation treatment or contra indications to radiation treatment.

3.2 Assessment of pathology:

3.2.1 Histological diagnosis of vulvar cancer.

3.2.2 Review of pathology from other institutions.

3.2.3 Tumor size, Stage, LN status, Depth of invasion, Margin, Vascular invasion.

3.3 Laboratory investigations:

3.3.1 CBC, electrolytes, creatinine, liver function studies.

3.4 Radiological investigations:

3.4.1 Chest x-ray or CT chest (if clinically indicated).

3.4.2 CT abdomen and pelvis (if clinically indicated).

3.4.3 MRI pelvis.

4. Staging: Based on TNM AJCC, 2010, 7th edition

5. Prognostic factors:

The most important is the presence and number of pathologically positive inguinal lymph nodes with 5 yr survival being 70-90% in node negative patients versus 25-41% in node positive patients. The other factors include:

5.1 Tumor size

5.2 Stage

5.3 Depth of invasion

5.4 Margin

5.5 Vascular invasion

6. Treatment:

6.1 Non-invasive disease

- Local excision

6.2 Invasive disease

6.2.1 Resectable primary Tumor and/or Inguinal Lymph Nodes

- No involvement of clitoris, urethra or anal sphincter, no or small bulk lymphadenopathy, no distant metastases.
- Surgical excision of primary tumor with at least 10 mm surgical (8 mm pathological) margin.
- Ipsilateral (lateralized primary tumor) or bilateral sentinel inguinal lymph node sampling.
- Adjuvant radiotherapy + concurrent cisplatin chemotherapy (40 mg/m^2) of the primary tumor site for high-risk features (positive or close pathologic margins <8 mm, lympho-vascular space invasion). Adjuvant treatment of the primary site may be deferred in cases where the primary site can be followed clinically and where further local surgery is likely to be feasible in the event of local recurrence.
- Adjuvant radiotherapy + concurrent cisplatin chemotherapy (40 mg/m2) of inguinal and iliac lymph nodes for high-risk lymph node feature (more than one positive inguinal lymph node or extra-nodal extension of disease).

6.2.2 Initially unresectable Primary Tumor and/or Inguinal Lymph Nodes

- Radiotherapy + concurrent chemotherapy.
- Clinical and radiographic assessment of primary tumor and lymph node response after 3-5 weeks of radiotherapy (27-45 Gy in 1.8 Gy daily fractions) + chemotherapy.
- If resectable after 3-5 weeks, surgical excision of primary tumor and lymph nodes followed by additional radiotherapy/concurrent chemotherapy based on high-risk primary tumor and/or lymph node surgical-pathologic features.
- If unresectable after 3-5 weeks, continue radiotherapy to a total dose of 63 Gy 1.8 Gy daily fractions with concurrent chemotherapy.

7. Radiotherapy Protocol:

7.1. External Beam: Planning technique

7.1.1 Patient preparation: As in cervical carcinoma.

7.1.2 Immobilization As in cervical carcinoma

7.1.3 Orientation and patient set up: The patient is asked to lie in the supine position with the thighs straight or in the frog leg position. The frog leg position has been used to minimize the bolus effect from skin folds.

7.1.3.1. Markings and reference points:

Tattoos placed in certain points around the primary tumor, prior to therapy, can be used for objective evaluation of response to the treatment and for subsequent evaluation for boost therapy with reduced fields.At the time of simulation, markers should be placed on the primary, the lymph nodes, and scars from previous surgery to document the extent of the disease. The introitus should be marked with radio-opaque material in all patients to aid localisation of the inferior border of the CTV or field margin.

7.1.4 Image acquisition: As in cervical carcinoma

7.1.5 Target definition:

7.1.5.1 3D-conformal RT:

7.1.5.1.1 Primary tumor CTV includes the gross disease and sub-clinical extension i.e 1 cm around the gross tumor.

7.1.5.1.2 PTV is 1 cm around the CTV.

7.1.5.1.3 Lymph node CTV includes the superficial and deep inguinal-femora lymph nodes, and the internal and external iliac lymph nodes (7mm margin around the vessels).

Lymph node PTV includes 5mm margin around the CTV.

7.1.5.1.4 Organs at risk: as in cervical carcinoma.

7.1.5.2 Conventional:

If the simulator is used, the superior border is placed above the acetabulum to include distal external and internal iliac nodes, the inferior border 2 cm inferior to the vulvar marker, and lateral borders defined by palpation to the outer inguinal ligament at the anterior superior iliac spine or to cover the femoral heads.

7.1.6 Technique:

- Radiotherapy to the vulva alone is delivered with the patient in the lithotomy position, using electron therapy with good apposition of the applicator and bolus to ensure adequate skin dose to macroscopic disease.

- Three dimentional conformal radiotherapy if using photon therapy to the vulva and lymph nodes is delivered while the patient in supine position. The target volume is irregular, lying anteriorly at the vulva and inguinal nodes, with deep extension to the femoral and pelvic lymph nodes.

7.1.7 Beam arrangements:

Treatment is usually given with conformal radiotherapy using four beams as this reduces toxicity compared with anterior and posterior opposing photon beams since bowel and rectum can be shielded. If opposing fields are used, unequal weighting, such as 2:1 anterior to posterior, may be used to increase dose to the anterior structures but this arrangement may give unacceptable hot-spots. Bolus may be needed to ensure adequate dose to gross primary tumour or positive surgical margins, particularly with the skin sparing effect of higher energy beams.

7.1.8 Beam energies:

6-18 MV + electron therapy.

7.1.9 Dose prescription and fractionation

7.1.9.1 Adjuvant radiotherapy:

7.1.9.1.1 Adjuvant radiotherapy to vulva alone, node negative, surgical margin less than 5mm

- Electron therapy:
  45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.

7.1.9.1.2 Adjuvant radiotherapy to vulva alone, node negative, residual macroscopic disease

- Electron therapy:

45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.

Boost to residual disease:
15 Gy in 8 daily fractions of 1.875 Gy given in 1 and 1⁄2 weeks.

Total dose:
60 Gy in 33 daily fractions given in 6 and 1⁄2 weeks.

7.1.9.1.3 Adjuvant radiotherapy to vulva, inguinal and pelvic nodes, node positive

- EBRT:

45–50.4 Gy in 25–28 daily fractions of 1.8 Gy given in 5–5 and1⁄2 weeks.

- Electron therapy:

Boost to inguinal nodes if multiple positive nodes or extracapsular spread:
15 Gy in 8 fractions of 1.875 Gy in 1and 1⁄2 weeks.

- Total dose:

60–65.4 Gy in 33–36 daily fractions given in 6 and1⁄2 weeks.

7.1.9.2 Primary radiotherapy to primary tumour and nodes (may be given as concurrent chemoradiation for inoperable, locally advanced disease)

- EBRT:

45–50.4 Gy in 25–28 daily fractions of 1.8 Gy given in 5–5 and 1⁄2 weeks.
Subsequently surgery is performed if possible or further radiotherapy to the primary tumour and involved nodes given.

- Electron therapy:

Boost to primary tumour and palpable nodes:
15–20 Gy in 8–11 daily fractions of 1.8 Gy given in 2 and 1⁄2 weeks

- Total dose:

60–65.4 Gy in 33–36 daily fractions.

7.1.9.3 Palliative treatment:

- Photon or electron therapy
- 20 Gy in 5 daily fractions given in 1 week.
- 30 Gy in 10 daily fractions given in 2 weeks.
- 8–10 Gy in a single fraction for haemostasis.

7.1.10 Dose limitation to OAR : Refer to cervix protocol.

7.1.11 Verification and plan execution: Refer to cervix protocol.

7.2 Brachytherapy:

Interstitial brachytherapyy may be useful as a boost treatment in selected patients, particularly if the lower vagina is involved by tumor.
Not available currently in referral center.

7.3 Sequelae of treatment

7.3.1 Acute and late sequelae: Refer to cervix protocol.

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7.3.2 Additional:

Late vulvar fibrosis and atrophy may occur and vaginal rehydrating gel can be helpful. Lymphedema can occur in up to 30 per cent of patients when inguinofemoral surgery and radiotherapy are combined. Urethral stenosis can also occur as a late effect. Limiting the total vulvar dose to 65 Gy or less reduces the risk of skin necrosis. There is an 11 per cent risk of necrosis of the femoral heads at 5 years, if opposing anterior and posterior beams are used in an elderly population.

8. Principles of hormonal Treatment:

Not applicable

9. Principles of Chemotherapy:

There is no standard chemotherapy for vulvar cancer, and reports describing the use of this modality in the setting of metastatic or recurrent disease are anecdotal. Extrapolating from regimens used for anal or cervical squamous cell cancers, chemotherapy has been studied in combination with radiation in the neoadjuvant setting or as primary therapy in advanced disease.

9.1 Concurrent:

Weekly cisplatin at 40 mg/m^2 as radiosensitizer.

9.2 As neoadjuvant therapy:

In more advanced disease, chemo might be given with radiation therapy before surgery. This combined treatment may shrink the tumor, making it easier to remove it with surgery. So far, the results of treating vulvar cancers that have spread to other organs with chemo have been disappointing. There is evidence that neoadjuvant chemoradiation with 5-FU plus either cisplatin or mitomycin-C may convert patients to more operable status, but the evidence base is limited by study design. In addition to a paucity of randomized trials, interpretation of these studies is complicated by the lack of a standard definition of inoperability.

10. Management of recurrence/relapse and metastatic disease:

There are four small studies of chemotherapy for patients with advanced, recurrent or metastatic vulvar carcinoma, not amenable to locoregional treatment. Chemotherapy has generally only been used in the salvage setting after surgery and/or radiotherapy, and the type of chemotherapy that was offered depended on the age, performance status and renal function of the patient.

10.1 Radiation in recurrence /relapse :

10.1.1 EBRT**:**
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.

10.1.2 Electron therapy:
Individualised boost:
15–20 Gy in 8–11 daily fractions of 1.8 Gy

10.1.3 Total dose
60–65 Gy in 33–36 daily fractions.

10.1.4 Recurrent disease in the inguinal region only, if patient not fit for pelvic radiotherapy. 50 Gy in 20 fractions using an individualised combination of photons and electrons.

11. Follow Up

11.1 3-6 weeks after competing radiotherapy for toxicity assessment.
11.2 Every 3 to 4 months for 1 to 2 years after competing RT, then every 6 months for 3 to 3 4 years, and annually after 5 years.
11.3 Close clinical examination and colposcopy to exclude new primary tumors.
11.4 CT and or MR imaging as clinically indicated.

12. Ongoing departmental studies:

Not Applicable

13. References:

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A.11- SOFT TISSUE SARCOMA CLINICAL MANAGEMENT GUIDELINES

1. Epidemiology:

Soft tissue sarcoma (STS) constitute a heterogeneous group of rare solid tumours of mesenchymal cell origin with distinct clinical and pathological features. Adult soft tissue sarcomas are rare tumors, represent 1% of adult malignancies and 15% of pediatric malignancies. In US the estimated new cases in 2016 is 12.310 cases. In GCC the ASIR is 1.1 per 100, 000 case. While in Kuwait, ASR is 0.6 in both male and female Kuwaiti patients.

2. Clinical Presentation:

2.1 The most common clinical presentation of soft tissue sarcoma is a slow-growing, painless mass. The median period between detection of the lesion and presentation to the clinician is approximately 4 months, and the clinician's delay in establishing the diagnosis is approximately 1 month.

2.2 Pain, numbness, and swelling may result from tumor invasion of bone or neurovascular bundles.

2.3 Although locally aggressive, they rarely extend into adjacent tissue compartments until late in the course of disease. Local spread can, however, be facilitated by surgical violation of tissue planes.

2.4 Approximately 6% to 10% of patients have metastatic disease at diagnosis. Hematogenous dissemination after diagnosis is common in high-grade lesions. Isolated pulmonary metastases are the most frequent, accounting for nearly 50% of all initial recurrence.

2.5 Bone, liver, and skin involvement occurred in less than 5% of patients. Liposarcoma and retroperitoneal sarcomas display a different metastatic pattern.

3. Diagnostic Work up:

3.1 Complete history and physical examination to assess performance status.

3.2 Complete blood count, liver and renal function tests.

3.3 Assessment of pathology

3.3.1 The standard approach to diagnosis consists of multiple core needle biopsies. However, an excisional biopsy may be the most Practical option for <5 cm superficial lesions.

3.3.2 An open biopsy may be another option in selected cases. The biopsy should be Performed by a trained surgeon, or discussed between the surgeon and the radiologist. It should be planned in such a way that the biopsy pathway and the scar can be safely removed on definitive surgery. It should be preceded by imaging [contrast-enhanced magnetic resonance imaging (MRI)] is the preferred method for limb and superficial trunk lesions.

3.3.3 Histological diagnosis should be made according to the World Health Organization (WHO) classification. The malignancy grade should be provided in all cases in which this is feasible based on available systems which distinguish three malignancy grades. The pathology report should include an appropriate description of:

3.3.3.1 Tumor size

3.3.3.2 grade

3.3.3.3 Tumor margins (i.e. the status of inked margins and the distance between tumor edge and the closest inked the surgical report should provide details on the surgical conduct with regard to possible contaminations (i.e. it should mention whether the tumor was opened, etc.).

3.3.3.4 If preoperative treatment was carried out, the pathology report should include a tumor response assessment. In contrast to osteosarcoma and Ewing's family of tumors, however, no validated system is available at present in this regard, and no percentage of residual viable cells is considered to have a specific prognostic significance. This depends on several factors, including the presence of non- treatment-related necrosis and hemorrhage and the heterogeneity of post treatment changes.

3.4 Adequate imaging of primary tumor is indicated for all lesions (MRI+/- CT)

3.4.1 A chest computed tomography (CT) scan is mandatory for staging purposes. Depending on the histological type and other clinical features, further staging assessments may be recommended (e.g. regional lymph node assessment for synovial sarcoma or epithelioid sarcoma, abdominal CT scan for myxoid liposarcoma, etc.).

3.4.2 Consider abdominal /pelvic CT for myxoid/ round cell liposarcoma, angiosarcoma, epitheliod sarcoma and leiomyosarcoma.

3.4.3 Consider MRI spine for myxoid/ round cell liposarcoma. Consider MRI CNS for Alveolar soft part sarcoma and angiosarcoma.

3.4.4 A multidisciplinary judgment is recommended.

4. Stagig TNM:

Staging according to the The American Joint Committee on Cancer (AJCC**, 7th** 2010)

5. Prognostic factors:

5.1 The most important prognostic factor for distant metastasis and survival is grade. For low-grade tumours, the risk of distant metastases at 5 years is <10%, compared with almost 50% for high-grade tumours.

5.2 Tumor size and depth are also prognostic with respect to distant metastasis. Certain histologic subtypes such as MPNST or leiomyosarcoma may be associated with increased distant metastasis and worse survival.

5.3 The presence of tumour cells at the surgical margin and inadequate surgical excision are the most important adverse risk factors for local recurrence.

5.4 Age >50 years, locally recurrent disease, MPNST or fibrosarcoma histology, the presence of symptoms at presentation, deep location, and withholding of radiation therapy have also been associated with increased local recurrence risk.

6. Treatment:

Soft tissue sarcomas are ubiquitous in their site of origin, and are often treated with multimodality treatment. Multidisciplinary treatment planning is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and pediatric oncologists if applicable).

6. 1 Surgery

6.1.1 Surgery is the standard treatment for all patients with adult type, localized soft tissue sarcomas. It should be performed by a surgeon specifically trained in the treatment of this disease. The standard surgical procedure is a wide excision.

6.1.2 Complemented by radiation therapy as standard treatment of intermediate-high grade, deep tumors with a diameter of >5 cm [II, A]. This implies removing the tumor with a rim of normal tissue around. One centimeter has been selected as a cut-off in some studies, but it is important to realize that the margin can be minimal in the case of resistant anatomic barriers, such as muscular fasciae, periostium and perineurium.

6.1.3 A marginal excision may be acceptable as an individualized option in highly selected cases, in particular for extra compartmental atypical lipomatous tumors.

6.2 Radiotherapy

6.2.1 While radiation therapy as an adjuvant to surgery is a standard for intermediate-high grade, deep tumors with a diameter of >5 cm, it is an option in selected cases of deep lesions less than 5 cm or low-grade tumors. Compartmental resection of an intracompartmental tumor, if performed, does not require adjuvant radiation therapy.

6.2.2 Radiation therapy should be administered postoperatively, with the best technique available, at a dose of 50–60 Gy, with fractions of 1.8–2 Gy, possibly with boosts up to 66 Gy, depending on presentation and quality of surgery.

6.2.3 Alternatively radiotherapy may be carried out preoperatively, normally using a dose of 50 Gy.

6.2.4 Intraoperative radiation therapy (IORT) and brachytherapy are options in selected cases.

7. Radiotherapy Protocol:

7.1 External Beam: Planning technique

7.1.1 Patient preparation

The day before simulation

No special preparation is required.

7.1.2 Immobilization

Immobilization techniques will vary with different tumor sites, but for the common tumors in upper or lower limbs, individually prepared vacuum bags or Perspex shells are used. Laser lights are used to minimize rotational movement, and craniocaudal movement should be prevented by appropriate foot or hand restraints

7.1.3 Orientation, set-up, marking and reference points

Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
Permanent ink (or tattoo) is applied to the lateral and midline reference Points.

7.1.4 Image acquisition

7.1.4.1 CT simulation

If possible, preoperative and pre-radiotherapy CT scans should be taken with the limb in the same position, and pre- and postoperative CT and/or MRI co-registered for planning. However, changes in muscle configuration following surgery and the position of the scar will alter appearances significantly and it is essential for surgeon and radiation oncologist to plan jointly all treatments for optimal local control and functional outcome.

7.1.4.2 Simulator

For palliation, treatment volumes can be defined in the simulator. The GTV is defined from CT information and the clinical assessment.

7.1.5 Target definition:

- The surgeon, oncologist and pathologist should meet to discuss the most likely sites of recurrence if adjuvant radiotherapy is to be considered.

7.1.5.1 GTV: Usaully RT is given post operatively, so GTV is determined from preoperative image and clinical finding.

7.1.5.2 CTV : Postoperatively a CTV must be designed which includes the initial GTV, any likely sites of tumour dissemination from surgery (such as scar) and a margin to encompass potential microscopic spread, which will vary for different tumor types from 20 mm to 50 mm.

Clips placed at surgery may be helpful. With improved imaging, **a GTV-CTV** margin of 50 mm is adequate in the vertical direction for phase I and then 20 mm in the boost phase while the margin will be 20 mm in the horizontal direction in both phases. Optimum treatment volume sizes are being studied (in the VORTEX trial). Incomplete excision of very large tumours (which may be 15–20 cm long in the limbs) may make the CTV planned this way prohibitively large, and it may not be possible to encompass scars and excision margins in full. EBRT may then be restricted to areas of bulky residual disease, for example around vessels or nerves.

7.1.5.3 **PTV: A CTV-PTV** margin of 5–10 mm is added for set-up variability. In sites (such as ribs) where respiration is important, techniques appropriate to these sites should be used.

7.1.5.4 OAR will also vary depending on the primary tumor site.

7.1.6 The Technique:

Three Dimentional conformal radiotherapy.

7.1.7 Beam arrangement:

- Beam arrangement will be according to the site and the volume of the target.

- Treatment plans will need to be individualized although simple arrangements of opposing or wedged pairs of beams may be used for limb lesions.
- Care should be taken in this case to leave a strip of normal tissue unirradiated on one or both sides of the limb to prevent late lymphoedema from fibrosis of lymphatic channels.
- Radiation to a joint should be avoided if possible.

7.1.8 Beam energies:

- Beam energy will be according to the site, depth, target volume.
- It can be photon or electron or mixed beam.

7.1.9 Dose prescription and fractionation

7.1.9.1 Adjuvant radiotherapy

66 Gy in 33 daily fractions given in 61⁄2 weeks (50 Gy as phase I then 16 Gy boost). This dose is recommended for maximal tumor control although it will be associated with a risk of functional impairment from fibrosis.

7.1.9.2 Preoperative radiotherapy

50 Gy in 25 daily fractions given in 5 weeks.
10–16 Gy in 5–8 daily fractions given in 5–10 days as a postoperative boost if The surgical margins are positive.

7.1.9.3 Palliative Radiotherapy

30 Gy in 10 fractions of 3 Gy given in 2 weeks.
20 Gy in 5 fractions of 4 Gy given in 1 week.

7.1.10 Dose limitation to OAR:

Dose limitation will be according to the site of the primary tumour.

7.1.11 Plan Verification and execution:

- The treatment iso centre on a DRR from the CT simulation is compared with portal images of the iso centre on the treatment machines using electronic portal imaging.
- Off-line correction protocols are used for standard conformal treatment.
- Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is _5 mm.

7.2 Brachytherapy:

Not used currently at referral center

7.3 Sequelae of treatment

7.3.1 Acute: dry and moist desquamation of the skin, delayed wound healing.

7.3.2 Late: fibrosis, contracture of the joint, oedema, pain, and bone fracture. In centres treating high volumes of patients with soft tissue sarcoma, the incidence of moderate-to-severe late effects is <10% (110). The risk of these complications may be reduced by sparing a strip of normal tissue (to allow lymphatic drainage from the extremity) and a portion of the circumference of uninvolved bone. If possible, joint spaces

should be excluded after a dose of 40 to 45 Gy to avoid fibrotic constriction of joint capsules. Collaboration with physical therapy specialists is essential in minimizing disabilities after treatment of soft tissue sarcomas. Mobility of the extremity should be stressed, and patients should be on an exercise and range-of-motion program early in the course of therapy.

8. Principles of Hormonal treatment:

Hormonal treatment is sometimes recommended as palliative measures in the treatment of metasatic endometrial stromal sarcoma.

9. Principles of chemotherapy:

Data have been provided that adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high risk patients (after a multidisciplinary judgment consensus). Most recently, a number of targeted therapies have shown promising results in patients with certain histologic types of advanced or metastatic STS.
Kindly refer to medical oncology guidelines.

10. Management of recurrence or relapse:

For patients with resectable, unresectable or disseminated recurrences, the guidelines recommend the same management after biopsy as outlined for the primary disease according to the previous treatment and the tolerance of the patient.
Palliative treatment for symptom control (RT, chemotherapy or surgery)and best supportive care are potential options that oncologists should discuss with symptomatic treatment.

11. Follow Up

11.1 During each follow up visit local symptoms, reactions and response is evaluated along with any new symptoms or complains or toxicity. Functional and cosmetic evaluation is also performed at regular interval by clinical assessment 3 - Follow up by regular CT scan / MRI of the treated sites is done for assessment of the treated site to R/O local recurrence.

11.2 Risk assessment based on tumour grade, tumour size and tumour site may help in hoosing the routine follow-up policy.

11.3 High risk patients generally relapse within 2–3 years, while low-risk Patients may relapse later, although it is less likely.

11.4 Early detection of local or metastatic recurrence to the lungs may have prognostic implications, and lung metastases are asymptomatic at a stage in which they are suitable for surgery. Therefore, routine follow-up may focus on these sites. The best method of follow-up has not been established.

11.5 MRI to detect local relapse and CT to scan for lung metastases is likely to pick up recurrence earlier, it is yet to be demonstrated that this is beneficial or cost effective compared with clinical assessment of the primary site and regular chest X ray.

11.6 The surgically treated intermediate/high grade patient may be followed every 3–4 months in the first 2–3 years, then twice a year up to the fifth year and once a year thereafter.

11.7 Low-grade sarcoma patients may be followed for local relapse every 4–6 months, with chest X-rays or CT scan at more relaxed intervals in the first 3–5 years, then yearly.

12. Ongoing Studies

Not Applicable

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A.12- HODGKIN'S LYMPHOMA CLINICAL MANAGEMENT GUIDELINES (ADAPTED FROM UHN, CANADA)

1. Epidemiology:

The estimated new cases in 2016 of Hodgkin's lymphoma according to the Seer data, is 8,500 cases. It is the ninth most common cancer in the GCC States. 3.146 HD cases (3.3% from all cancers) were reported from all GCC States during the ten-year period (1998-2007). The overall ASRs in 2009 were 2.2 and 1.6 per 100,000 populations for males and females respectively.

HD incidence was more common in men compared to women in all of the GCC States. Qatar had the highest incidence among men and Kuwait ranked second followed by Oman. It accounts 4% of GCC in all ages (1998-2007).

In Kuwait the over all ASIR in 2012 was 4.2 in male and 2.9 in female patinets. In non kuwiati it was 1.2 and 4.7 respectivly.

The age-incidence curve in developed countries is characterized by a bimodal distribution with aninitial peaks at around age 25 years and a second peak at age 60 to 70 years, in which a male predominance is observed.

The etiology of Hodgkin's lymphoma is unresolved. A combination of genetic susceptibility:

- Immune response impairment, and environmental exposures, are likely to play a central role in the pathogenesis of the disease. I
- Infectious causes: Epstein-Barr virus (EBV): Infectious mononucleosis, in which EBV is the causative agent, are at an approximately threefold increased risk for Hodgkin's lymphoma. In about one-third to half of cases of classical Hodgkin's lymphoma occurring in Western populations, the monoclonal EBV genome can be detected in the Reed-Sternberg cells. EBV positivity is predominantly associated with the MC subtype, which is more common among young children and older adults, and is less frequently associated with NS cases seen mostly in young adults in the developed world.
- Genetic susceptibility: A five folds increased risk has been demonstrated in first-degree relatives, and siblings of young adults with Hodgkin's lymphoma have a sevenfold increased risk. The excess risk appears to be more pronounced in same-sex siblings, which may be related to shared environmental exposure. Monozygotic twins of patients had an almost 100-fold increased risk, whereas no increased risk for dizygotic twins was observed, supporting the contribution of heritable factors to the development of the Hodgkin's lymphoma.

2. Clinical Presentation:

2.1 Painless lymphadenopathy: lymph nodes are rubber like and painless. They grow slowly. The most common site is the cervical region (80%). Axilla and inguinal involvement is rare. An anterior mediastinal mass is frequently seen (50%), mediastinal involvement is common in nodular sclerosis type HD.

Hepato- splenomegaly is uncommon. Splenic involvement is seen in all cases with bone marrow and hepatic involvement.

2.2 B symptoms: Present in 1/3 of cases.

2.1.1 Fever (due to increase in inteleukins 1 &2. should be of unknown origin& above 38 degree Celsius).
2.1.2 Weight loss (more than 10% in last 6 months).
2.1.3 Drenching night sweets (due to increase in inteleukins 1 and 2).
2.1.4 In addition, itching and pain after alcohol intake may be observed.

3. Diagnostic Work up:

3.1 Full history.
3.2 Physical examination and assessment of ECOG PS, all lymph nodes site, size, number with examination of the Waldeyer's ring , Liver and Spleen.
3.3 Laboratory tests: CBC, ESR, albumin, LDH, LFTs, RFT (Urea, creatinine), TSH, HIV test if risk factor(s) present, viral markers, pregnancy tests in women of childbearing age, semen cryopreservation for young male if chemotherapy or pelvic radiotherapy will be planned.

3.4 Imaging studies:

3.4.1 CT head and neck, thorax, abdomen and pelvis.
3.4.2 Gallium scan or FDG-PET scan.
3.4.3 MUGA scan (in patients considered for chemotherapy)
3.4.4 Additional imaging tests, e.g. MRI, bone scan, ultrasound, as determined by symptoms or clinical situation.

3.5 Histopathology:

3.5.1 Excion biopsy of lymph node with immunohistochemistry/core biopsy may be adequate if sufficient sample/ FNAC is inadequate / review of pathology at referral center.

3.5.2 Assessemnt of the histopatological type**:**

3.5.2.1 HD is histologically characterized by presence of diagnostic multinucleated giant cells (Reed Strenberg cells, CD 15+ and CD 30+) within a mixed inflammatory infiltrate (lymphocytes, plasma cells and eosinophils), and it originates from lymphoid system.

3.5.2.2 Nodular lymphocyte predominance Hodgkin's lymphoma (NLPHL, 2- 5%) is positive for CD45 and CD20.

3.5.2.3 Classical Hodgkin's lymphoma (95%) is positive for CD15 and CD30 and has 4 subtypes:

- Nodular sclerosis (65%).
- Lymphocyte-rich (10%).
- Mixed cellularity (20%).
- Lymphocyte depleted type (<5%).

3.5.3 BM aspirate and biopsy not routinely required, unless one or more of the following are present:
3.5.3.1 B symptoms.
3.5.3.2 Abnormal CBC (cytopenias).
3.5.3.3 Stage III/IV disease.
3.5.3.4 HIV positive.
3.5.3.5 Age > 60 (mixed cellularity histology).
3.5.4 PFT in case of mediastinal or lung irradiation.

3.6 Assessment of the International Prognostic score (IPS) for advanced disease

3.6.1 Albumin (<4g/dl).
3.6.2 Hb (<10.5g/dl).
3.6.3 Male.
3.6.4 Age≥45yrs
3.6.5 Stage IV disease
3.6.6 WBC >15000/mm3
3.6.7 Lymphocyte count <8% of WBC or ALC <600/mm^3

3.7 Patient and family counseling:

3.7.1 Physical and psychological health issues, including impact of treatment on the quality of life, reproduction, cardiovascular fitness, risk of recurrence, and risk of second malignancies.
3.7.2 Smoking cessation for smokers. Attention to screening for colorectal cancer and lung cancers (patient may be study-eligible).
3.7.3 Ensure appropriate advice and care from family doctor or cardiologist: Cardiac risk factors and strategies to minimize risk (smoking cessation, BP, cholesterol, lipids, exercise, weight control), particularly for patients who received mediastinal radiation.

4. Staging:

Please refer to Cotswolds lymphoma staging (1989) (Modified Ann Arbor staging system). For additional information of HD staging, refer to the Lugano classification, 2014.

5. Prognostic factors:

5.1 Histological sub type.
5.2 Stage of the disease.
5.3 B symptoms carry poor prognosis in all stages.
5.4 Risk group for all HD:
5.4.1 **Early favourable:** clinical stage I or II without any risk factors.
5.4.2 **Early unfavourable**:
5.4.2.1 Clinical stage I or II with one or more of the following risk factors. Large mediastinal mass, extra-nodal involvement, elevated ESR (>30 mm/hr for B stage, > 50 mm for A stage).
5.4.2.2 Involvement of more than 3 lymph node regions.
5.4.2.3 B symptoms.

5.4.3 **Advanced favourable:**
Clinical stage III or IV with 0-3 of the risk factors listed below:
5.4.3.1 Albumin level of less than 4.0 gm/l.
5.4.3.2 Hb level of less than 10.5 g/dl,
5.4.3.3 WBC counts more than 15000 /cc.
5.4.3.4 Male sex.
5.4.3.5 Age 45 yrs or more.
5.4.3.6 Stage IV disease.

5.4.4 Advanced unfavourable: Clinical stage III or IV with 4 or more of the adverse factors listed above.
5.4.4.1 Low risk IPS0-3
5.4.4.2 High risk IPS 4-7

6. Treatment:

6.1 Early-stage Hodgkin's lymphoma:

Combined modality therapy: Advantages of combined-modality therapy over RT alone include the significantly higher disease-free survival (DFS) that has been demonstrated in several randomized trials and the avoidance of large-field RT. Current data suggest that involved-field radiation therapy (IFRT) is adequate when given as part of combined-modality therapy.

6.1.1 Stage I/II Hodgkin's Lymphoma

Risk-adapted treatment recommendation based on categorization into the following groups:

6.1.1.1 Nodular Lymphocyte Predominant HD

If stage I, low bulk (< 5 cm) in peripheral nodal area: Involved field RT 35 Gy in 20 fractions.

6.1.1.2 All other NLPHL: treated with combined modality therapy as per guideline for very favorable or unfavorable, depending on clinical assessment and staging results (see below).

6.1.1.3 Very Favorable group:

For stage IA and II patients GHSG HD10 eligibility requires that non of the following clinical risk factors are present:

- Large mediastinal mass (>1/3rd of thoracic diameter).
- ESR ≥ 50 without B symptoms or ESR ≥ 30 with B.
- Extranodal symptoms.
- ≥ 3 lymph node regions involved.

ABVD x 2 cycles and 20Gy involved field RT in 20 Fractions
Alternate treatment plan (to avoid IFRT, e.g. young female with Axillary disease), ABVD x 2 cycles, restage with CT-PET, if in CR, continue with 2 additional cycles of ABVD without radiation.

6.1.1.4 Early stage IB, IIB unfavorable (adapted from NCIC and GHSG):

- Bulky mediastinal mass (med width/thoracic diameter > 1/3, or bulk > 10 cm).
- Extranodal extension (lung, chest wall, pericardium).

- >3 nodal sites.
- Unexplained anemia.

ABVD x 4 (for bulky mediastinal disease: 6 cycles) + involved field
RT 30 Gy in 20 fractions. 35 Gy may be considered for bulky site, and /or significant residual mass > 5 cm, although there are limited data indicating a dose response > 30Gy in the adjuvant setting.

6.1.1.5 Alternate treatment plan (to avoid IFRT, e.g. young female with many nodal sites including, axilla in patients without bulky disease):

ABVD x 2 cycles, restage with CT-PET (provincial registry study), if in CR, continue with 4 additional cycles of ABVD without radiation.

6.2 Advanced-stage Hodgkin's disease:

Chemotherapy, the ABVD regimen, however, there have been recent promising data on more dose-dense and dose intense regimens, including the dose-escalated BEACOPP and Stanford V regimens. **The role of RT in patients with advanced-stage Hodgkin's disease is limited**. Most of the randomized trials do not show a significant benefit with the addition of RT to chemotherapy.
However, there are subgroups of patients who may benefit from consolidative RT, namely, patients who failed to achieve a complete response to chemotherapy and those with bulky disease at presentation.

6.2.1 Stage III and IV Classical and NLP HL

6.2.1.1 **Chemotherapy: ABVD X 6-8 cycles (treat to 2 cycles beyond best response).**
Restaging with CT and PET post cycle 3 and 6 consider escalated BEACOPP for 6-8 cycles.

6.2.1.2 Involved field RT 30-35 Gy in 20 fractions for bulky site > 10 cm. at presentation and PR following completion of primary chemotherapy.
Optional: CT-PET scan at the end of therapy if residual disease > 2.0 cm. if PET positive (though a minimum of PR response by CT criteria), proceed with IFRT 30-35 Gy in 20 fractions to PET avid site of disease.

NB: For all stages, restaging using PET/CT scan and 5- point Deauville criteria should be done and further therapy depends on the results.

7. Radiotherapy Protocol:

7.1 External Beam: Planning technique

7.1.1 Patient preparation (rectal and bladder status), if abdomen/pelvis in the field

7.1.1.1 The day before simulation

Patient should avoid eating large amount of fruits and vegetables, beans and dairy products.

7.1.1.2 The evening before simulation

Patient should take two tablespoons of laxative. This will help in bowel movements.

7.1.1.3 The day of simulation

Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products. If he/she have not had a bowel movement in the past 16 hours, then he/she should take another two table spoons of laxative.

7.1.1.4 One hour before simulation

Patient should evacuate the bladder and drink 500 cc of water before simulation to make bladder full (at least 70%). Repeat this bladder filling process before each of daily radiation treatments.

7.1.2 Immobilization

7.1.2.1 Use of Orfit to relevant site for proper immobilization.
7.1.2.2 Knee & Ankle support, Alfa cradle if available will improve immobilization.

7.1.3 Orientation, set-up, marking and reference points

7.1.3.1 Patients lie in the comfortable position as per the site to be irradiated.
7.1.3.2 A standardized bladder/retum protocol is used for planning and treatment as mentioned earlier for patients with abdominal/pelvic sites.
7.1.3.4 Patient aligned with 3 laser beams. Set 3 marks on the patient skin. The middle one usually in the midline.
7.1.3.5 Permanent ink (or tattoo) is applied to the lateral and midline reference points.

7.1.4 Image acquisition

Conventional Simulation

7.14.1 Conventional simulation is used in selected cases of head & neck & inguinal areas. If AP beams are to be used for palliation, the borders can be defined in the x-ray simulator. The beam centre is marked with a reference tattoo and the borders are drawn on the skin fluoroscopy can be used to view tumour movement if IGRT implemented later on.

7.1.4.2 CT simulation: Majority of cases are treated with CT based 3D conformal plans.

- CT examination is performed on a spiral CT scanner using a slice thickness of 3 mm.
- Slices range acquired are different according to the treatment site.
- An isocentre is tattooed in the CT scanner, as are lateral reference points.

7.1.4.3 PET/CT simulation: A co-registered PET scan can be used to aid volume definition

7.1.5 Target definition

Nodal Sites:

7.1.5.1 GTV:

The residual GTV following chemotherapy, defined by PET-CT, could be the basis of the target volume.

➢ ***Involved Field Radiotherapy (IFRT):***

Involved field radiotherapy limits radiation delivery to the lymph node region involved with macroscopic lymphoma. Uninvolved nodal regions are not covered intentionally, but partial coverage of these regions may result from the allowance of adequate margins for the involved nodal region(s).
For patients having previous chemotherapy, it is limited to the post chemotherapy volume in all directions except cranio-caudally, where the pre-chemotherapy volume is used. It is based on the anatomical node region involved. Thus involved field would include the entire neck including the supraclavicular fossa when a neck node was involved, entire mediastinum and supraclavicular nodes for mediastinal involvement, entire para-aortic chain for para-aortic node disease and typically inguinal and ipsilateral iliac nodes for groin node disease.

- Uninvolved lung hila no need to be covered.
- Uninvolved cervical lymph nodes above the level of the larynx no need to be routinely covered.
- Uninvolved subcarinal and posterior mediastinal lymph nodes no need to be covered.

7.1.5.2 Clinical Target Volume:

The pre chemotherapy imaging is used to define the superior and inferior extent of original disease, which is expanded cranio-caudally by a margin of 1.5 cm. in the direction of potential lymphatic spread. It is not necessary to encompass entire nodal regions or adjacent areas.
In the transverse plane, the CTV will include the involved only nodes (or organ) and any residual disease (not the whole pre chemotherapy volume). The CTV should not extend into air, muscle planes or bone, unless the lymphoma is invading muscle or bone.

➢ ***Involved Site Radiotherapy: (ISRT):***

Further steps to reduce the radiation volume treated and hence the probability of late effects have resulted in the concept of involved site radiotherapy. It is based on defining the site of gross disease pre-chemotherapy and using a CT based volume treating the original disease with an expansion to form a CTV in the cranio-caudal direction and the post chemotherapy involved nodal chain and residual disease to form the CTV in all other directions.

➢ ***Involved Node Radiotherapy (INRT):***

It defines the pre-chemotherapy extent of disease as the CTV for post chemotherapy radiation without the need for a margin. Patients are required to have a pre chemotherapy PET-CT in the planning position to achieve this. We are using PET based plan in cases where there is a residual disease after completion of planned chemotherapy.

N.B: If there is residual GTV, extent of the GTV is defined clinically, PET/ CT and CT scan images. In such cases, a direct 3D expansion from the GTV will often need to be extensively edited to constrain the volume with the nodal chain as well as air and tissue planes. In the case of pre-chemotherapy imaging not being available, the patient should be treated using IFRT.

- *Supra-diaphragmatic Sites:*
  These will include cervical nodes, supra-clavicular fossae (SCF) axillae, mediastinum and hilum.

- *Infra-diaphragmatic sites:*
  These will include para-aortic (PA) nodes, mesenteric nodes, spleen and splenic hilum and iliac and inguinal nodes. If PA nodes are to be treated with the spleen / splenic hilum, a single volume may be used to encompass all sites. If adjacent nodal regions are involved, these may be treated with large fields. Alternatively supra and infra diaphragmatic fields may be treated consecutively with a calculated gap between the two and leaving a two to three week interval between treatments. Care is needed when matching supra and infra diaphragmatic fields to avoid overlap.

7.1.5.3 Planning Target Volume:

The CTV will be expanded further to create the PTV to account for organ and set up errors. CTV to PTV margins should be defined individually for each disease site and treatment centre depending upon their technique, set up accuracy and consideration of internal organ motion. Typical margins are as follows:

7.1.5.3.1 Head & Neck – 0.5 to 1 cm. depending on local set up.

7.1.5.3.2 Mediastinum – 1 cm. transversely and 1.5 cm. cranio-caudally.

7.1.5.3.3 All other sites – 1 cm.

7.1.5.4 OAR contouring: as per anatomical sites

Extra-nodal sites:

The principles og GTV discussed in the nodal lymphoma guidelines will also be applied to irradiation of extra nodal sites. In general, the **CTV** will include the entire organ affected. Examples of common sites are:

- *Head & Neck:*
  Conventionally lymphoma arising in any part of Waldeyer's ring will be treated with inclusion of all sites of Waldeye's ring in the radiation field. There is no good evidence of depart from this practice at present, thus whilst a limited GTV may be defined the CTV will include the entire ring from nasopharynx to lingual tonsil. If the disease occurs anywhere in the maxillary antrum, bilateral region will be outlines from base of orbital roof to base of maxillary bone to make the CTV. Parotid lymphoma will be treated using a CTV which includes the entire ipsilateral gland.

- *Stomach & Spleen:*
  The entire organ as defined on CT imaging will constitute the CTV. Allowance for organ motion is important in defining the CTV to PTV expansion, in particular cranio-caudally is recommended.

- *Bone:*

Ttraditionally the entire bone has been included in the treatment volume. Where a GTV can be defined then the CTV should include the entire width of a bone and cranio- caudally allow a minimum of 3 cm. margin along the bone marrow cavity.

- *Brain:*

Cerebral lymphoma is characteristically diffuse in nature and the CTV should include the whole brain from base of brain stem to frontal, parietal and occipital lobes.

- **Planning Target Volume:**

This will require expansion of the involved node CTV to allow for set up errors and internal organ motion. The same guidelines apply for involved site PTVs. However, particular areas to be aware of are the spleen and stomach, where respiration requires a larger expansion, particularly in the superior and inferior directions, (20 mm is recommended). Treatment fields will also include the PTV with a margin for penumbra.

7.1.6 The Technique:

Three dimentional conformal radiotherapy.

7.1.7 Beam arrangement: Depends upon the site treated, AP/PA or multiple fields.

7.1.8 Beam enrgies: Depends upon the site treated, and separation, it ranges from 6 to 18 MV.

7.1.9 Dose prescription and fractionation

7.1.9.1 Combined modality therapy:

Non bulky stage I-II 20-30 Gy if treated with ABVD, 30 Gy
if treated by STANFORD V.
Non bulky stage IB-IIB 30 Gy/ 20 f.
Bulky sites all stage 30 – 36 Gy.
PET scan Deavuille 3-4 following chemotherapy 30-45 GY

7.1.9.2 RTalone (uncommon except in NLPHL)

Involved region 30- 36 Gy
Uinvolved region 25- 30 Gy

- Treatment will be delivered once daily, 5 fractions per week, over 5 to 5.5 weeks.
- For undetectable disease after short course chemotherapy, i.e. CR, the clinician may choose to lower the dose to 20 Gy in 10 fractions.

7.1.10 Dose limitation to OAR: *Tabe (A.12.a).*

OAR	Limiting Dose / Volume
Brain stem	**Maximum dose of 50 Gy. to any part of the volume.**
Breast	**Minimise volume inside PTV, particularly in young women.**
Heart	**D100 of 30 Gy, V33 < 60% ; V38 < 33% ; V42 < 20% (13)**
Kidney	**V40 of 40% - if single kidney irradiated V15 of 65-70%. If both V15 of 20-25% for each kidney.**
Lens	**Maximum dose of 6 Gy to any art of the volume.**
Liver	**V40 of 30-35% D100 of 20 Gy.**
Lung (whole)	**V20 of 35%**
Optic chiasm	**Maximum dose of 50 Gy. to any part of the volume.**
Optic nerve	**Maximum dose of 50 Gy. to any part of the volume.**
Ovary	**Maximum dose of 10 Gy. to any part of the volume outside PTV. If inside PTV, discuss individual case with clinician. Considering ovaryplexy in pre-menopausal women.**
Parotid	**Maximum dose of 32 Gy to any part of the volume outside the PTV of the contra-lateral parotid.**
Spinal cord	**Maximum dose of 40 Gy. to any part of the volume.**
Testis	**Maximum dose of 2 Gy to any part of the volume.**

7.1.11 Verification and plan execution:

- Plan approval should be done by a senior oncologist in presence of the concerned physicist and a radiation oncologist.
- Ideally the treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- Portal images are taken on the first 3 days of treatment, using EPIs or portal films and compared with simulator or DRR images.
- Any systematic errors of more than 3 mm are identified and corrected, and weekly EPIs then taken.
- Treatments in large patients may show a high random error and then daily portal imaging may be necessary.

7.2 Brachytherapy:

Not Applicable.

7.3. Sequelae of treatment

7.3.1 Acute:

Acute Radiotherapy toxicities are variable according to the irradiated site. Mucositis, dermatitis, dysphagia, radiation pneumonitis, ect.,. It is assessed and scored according to RTOG-EORTC scoring system.

7.3.2 Late:

7.3.2.1 Most important long term toxicities include secondary malignancies (leukaemia, lymphoma and solid tumours) and cardiovascular diseases (coronary artery disease, pericarditis etc).

7.3.2.2 Subclinical hypothyroidism Azoospermia in males and ovarian dysfunction in females after Pelvic irradiation can occur.

8. Priciple of Hormonal therapy:

Not Applicable

9. Principle of Chemotherapy:

9.1 ABVD is the commenst regimen +/- Rituximab
9.2 Stanford V.
9.3 Escalated BEACOPP
9.4 Escalated BEACOPP followed by ABVD
9.5 CHOP +/- Rituximab
9.6 CVP Rituximab

Kindly refer for the detailed medical oncology guidelines of chemotherapy for HD.

10. Management of recurrence or Relapse:

10.1 Chemotherapy regimen:

10.1.1 C-MOPP (Cylophosphamide, vincrisyine, procarbazine, prednisone).
10.1.2 ICE (Ifosfamide, Carboplatin, Etoposide).
10.1.3 ESHAP (Etoposide, Methyl prednisolone, High dose Ara C, Cisplatin).
10.1.4 DHAP (Dexamethasone, High dose Ara C, Cisplatin).
10.1.5 GVD (Gemcitabine, Vinorelbine, Liposomal Doxorubicin).
10.1.6 GCD (Gemcitabine, Carboplatin, dexamethasone).
10.1.7 MINE (Mitoxantrone, Ifosfamide, Etoposide).
10.1.8 Brentuximab vedotin is an option in patient if HDT/ASCR has failed or at least 2 prior mutiagent therapy has failed.

10.2 Primary refractory disease: High dose chemotherapy+ stem cell transplantion.

10.3 Relapse: Previous RT 15-20 Gy RT.
No previous RT 30-40 Gy RT.

10. 4 Relapse in stage III-IV cases: Autologous bone marrow transplantation (BMT) or stem cell transplantation.

11. Follow up:

11.1 During RT: Weekly review in OPD with CBC and for assessemnbt of treatment toxicity which is variable according to the treatment site.
All toxcicity are graded according to RTOG-EORTC scoring system.

11.2 Response assessment at 3 months post treatment:

11.2.1 Document with PET/ CT of previously involved areas; gallium or PET scan may be indicated if not change from end-of-treatment scans.

11.2.2 At each subsequent visit:
Document history and physical examination, document toxicity, measure CBC if blood counts have not returned to normal at prior visit, (add TSH every 6 months if radiation to thyroid gland). Consider repeat imaging study only if new symptoms suggesting possible disease recurrence. Patients with previously demonstrated stable post-treatment masses, no need to be followed with CT scan if asymptomatic.

11.2.3 Consider cardiac stress test for 10-year survivors who received mediastinal RT, particularly if other cardiac risk factors exist.

11.2.4 For women who had radiation therapy to breast tissue: screening mammography and/or MRI (at recommendation of radiologist or ACR guideline) starting 8-10 years post treatment, or age 30, whichever comes later. MRI + mammogram is recommended for survivors under age 40. Patients >40 years old may have MRI discontinued at the discretion of the oncologist and radiologist depending on mammographic density. Survivors over age 50 can be screened with mammography alone.

11.2.5 Oncology Clinic Follow-up Frequency:

- First year - Visits every 3 months.
- 2 - 3 years - Visits every 4 months.
- 4 - 5 years - Visits every 6 months.
- > 5 years - annual follow up

In general, alternate follow up visits between attending medical Oncologist/haematologist and radiation oncologist. Family physicians are encouraged to participate in the follow up as outlined, particularly for visits beyond 5 years from treatment.

12. Ongoing Departmental studies:

Not applicable.

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A.13- Non Hodgkin's Lymphoma
CLINICAL MANAGEMENT GUIDELINES (ADAPTED FROM UHN, CANADA)

1. Epidemiology:

1.1 NHL is a group of more than 30 lymphoproliferative malignancies with different epidemiology, natural history and treatment approaches and outcome. Pertinent pidemiological facts about NHL are as follows:

1.1.1 The incidence of NHL is rising rapidly.
1.1.2 Gender: Male to female ratio of NHL is 1.5 to 1.0.
1.1.3 Age: NHL rises exponentially with age.
1.1.4 Race: Caucasians have a higher incidence than blacks.

1.2 The Estimated New Cancer Cases in 2012 was 235,700 world wide. It is more common in developed regions, with the highest incidence ASR found in Australia, with ASR (9.1 per 100, 000).

1.3 In US, the estimated new cases in 2016 is 72, 580.

1.4 NHL is the third most common cancer in the GCC States. There were 7,087 NHL cases reported from all GCC States accounted to 7.4% from all cancers diagnosed during the period from 1998 to 2007.

1.5 The overall ASIRs for all GCC States were 6.5 and 4.8 per 100,000 populations for males and females respectively between1998-2007.

1.6 In Kuwait, in 2012, the ASIR was 7.4 cases /100,000 and 8.3 cases /100,000 populations for male and female Kuwaiti repectivly. In non Kuwaiti ASR was 3.6 and 3.8 respectively.

2. Clinical Presentation:

2.1 Painless lymphadenopathy: The most common site for LAP is the cervical region (70%), groin (60%) and Axilla 50%). Hepato-splenomegaly is common. Splenic, bone marrow and hepatic, GIT and CNS involvement is much more common than HL.

2.2 B symptoms:

2.2.1 Present in 20-30 % of cases,
2.2.2 Fever (due to increase in inteleukins 1 &2), should be of unknown origin & above 38 degree Celsius).
2.2.3 Weight loss (more than 10% in last 6 months).
2.2.4 Drenching night sweets (due to increase in inteleukins 1 and 2).

2.3 Other symptoms may be present based on the site of disease and extranodal origin.

3. Diagnostic Work up

3.1 Full history including systemic symptoms (unexplained fever, night, sweats, weight loss > 10% of body weight), risk factors for HIV infection.
3.2 Physical examination:
3.2.1 Performance status.
3.2.2 Special attention to lymphatic sites, including Waldeyer's ring and presence of organomegaly.

3.2.3 For palpable lymph nodes: note and record, number, size, location, shape, texture, and mobility.

3.2.4 Mirror examination of larynx and pharynx if clinically indicated.

3.3 Laboratory tests: CBC, ESR, albumin, LDH, LFTs, RFT (Urea, creatinine), TSH.

3.4 Special tests: Standard:

3.4.1 Bone marrow biopsy (minimum unilateral iliac crest).

3.4.2 Review of slides by expert hematopathologist.

3.4.3 Cytologic evaluation, if any effusion present.

3.4.5 Lumbar puncture to examine cerebrospinal fluid for protein, glucose, cell count and cytology for perimeningeal sites, testes, extradural presentations, for those considered at risk for CNS involvement or when clinically indicate.

3.4.6 Pregnancy testing in women of childbearing age (if chemotherapy is planned).

3.4.7 Discussion of fertility issues and sperm banking.

3.4.8 Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy and chemotherapy.

3.5 Imaging studies:

3.5.1 CT head and neck, thorax, abdomen, pelvis.

3.5.2 Gallium scan or FDG-PETscan.

3.5.3 MUGA scan or Echocardiogram (in patients considered for doxorubicin, Age > 60 yrs or those with risk factors for cardiovascular disease).

3.5.4 Additional imaging test(s), e.g. MRI, bone scan, ultrasound, as determined by symptoms or clinical situation.

3.5.5 BM aspirate and biopsy for morphology, flow cytometery, cytogenetic/ FISH depending on histology.

3.6 Pathological assessment

3.6.1 Review of pathology at referral center.

3.6.2 Adequate immunophenotyping to establish the diagnosis.

3.6.3 Cytogenetic or molecular genetic analysis under certain circumstances to identify specific chromosal translocation.

3.6.4 Biopsy for proper histopathological classification (following WHO NHL classification system, 2008).

3.7 Assessment of the different risk group based on the different HP types (NCCN guidelines version 2.2016) e.g.

3.7.1 FLIPI 1 for follicular lymphoma.

3.7.2 IPI for DLBCL.

3.7.2 NK/T–Cell lymphoma nasal type index.

3.8 Re-Staging Investigations:

(Applicable for patients receiving combined modality therapy, to document response after recieving chemotherapy, prior to radiation therapy)

3.8.1 Physical examination.

3.8.2 When physical examination is unable to determine response, the appropriate imaging test(s) will be done to document response. A complete or partial response is required to proceed to planned radiation therapy (by CT scan +/- functional imaging). A less than partial response may require alternate treatment strategy.

3.8.3 Biopsy may be needed to confirm HP.

4. Staging:

Using Lugano modification of Ann Arbor staging system, 2014.

5. Prognostic factors:

5.1 Histological sub type is prime determinant of survival in NHL. Agreesive h**istology Lymphomas are**:

- 5.1.1 Diffuse large cell B cell type lymphoma (Include transformed follicular and transformed MALT) and variants (T cell rich B cell lymphoma.)
- 5.1.2 Primary mediastinal lymphoma.
- 5.1.3 Follicular Grade 3 B lymphoma.
- 5.1.4 T-cell: anaplastic large cell lymphoma.
- 5.1.5 Peripheral T cell lymphoma and variants (angiimmunoblastic T cell, ALCL ALK negative etc).
- 5.1.6 Mantle cell lymphoma.
- 5.1.7 Extrandoal NK.
- 5.1.8 Burkitt's lymphoma.

5.2 Big tumor Bulk > 7.5 cm.

5.3 Advanced stage of the disease.

5.4 B symptoms carry poor prognosis, relatively less significant than in HD.

5.4 IPI: includes patient's parameters like age (less or over 60 yrs), performance status, number of involved extranodal sites involvement and lactate dehydrogenase levels, etc are considered important prognostic factors in NHL.

5.6 Prolifertaive index: S-phase fraction <5% and KI-67 <80% are of favourable prognosis.

5.7 LDH level.

5.8 High B2 microglobulin level.

5.9 High CD44 expression.

5.10 Absence of BCL6 arrangment.

5.11 Sit of extranodal presentation (Brain and Testis carries wors brognosis).

5.12 Risk group.

6. Treatment:

The main modalities used to treat NHL are chemotherapy and radiation therapy, with surgery limited to secure the diagnosis or manage selected extranodal sites.

The initial decision in curative situations is between the use of local treatment alone versus a local and systemic approach. The choice is based on recognition of the potential for local control, inherent risk of occult distant m disease and availability of curative chemotherapy.

6.1 Treatment by stage and HP subtypes

6.1.1 Stage I/II Diffuse Large B cell lymphoma

Risk-adapted therapy, treatment recommendation based on the presence or absence of the following prognostic factors:

6.1.1.1 IPI factors: Age > 60
Abnormal LDH
Stage II

6.1.1.2 Tumor size: Bulk > 5 cm

6.1.1.3 Extranodal: testis, bone, epidural

Treatment:
No risk factors: **R-CHOP x 4 cycles IF RT 35 Gy in 20 fractions**

≥ 1 factor(s): **R-CHOP x 6 cycles**
IF RT 30 Gy in 20 F (35 Gy if initial bulk > 5 cm)

Optional: For patients achieving CR after 4 or 6 cycles of R-CHOP, observation with no RT should be discussed as a reasonable alternative, particularly if the following features are present:

- non-bulky (< 5 cm) presentation
- prior surgical excision of all gross disease (e.g. tonsil, splenectomy)
- multiple nodal regions involved (> 3), particularly if non-contiguous

6.1.2 Stage III/IV Diffuse Large B cell lymphoma

Treatment: **R-CHOP x 6-8 cycles (2 beyond CR)**
CT scan after cycle 3 and 6; functional imaging scan (gallium or FDG-PET) for residual imaging abnormalities at end of treatment >2 cm.

If residual mass post completion of systemic chemotherapy is FDG avid, consider biopsy and salvage chemotherapy and stem cell transplant if biopsy is positive. For those not eligible for stem cell transplant, and if the residual mass is localized, radiation may be considered (35 – 40 Gy in 20 fractions).

Radiation is not considered standard for patients with advanced DLBCL and is currently being investigated in prospective clinical trials. However, in certain clinical circumstances, involved field radiation may be appropriate, to reduce the risk of local recurrence or decrease future morbidity. Such circumstances include but is not limited to patients presenting with bulky masses (> 10 cm), extradural tumour with spinal cord/nerve root compression, impending or actual organ compromise (orbit, airway, long bone or weight-bearing bone fracture, etc).

6.2 Peripheral T cell lymphoma and variants (including Anaplastic Large Cell lymphoma):

Chemotherapy and radiation treatment recommendations are derived by extrapolation from results in aggressive B cell lymphomas or from retrospective analyses of large case series of PTCL. In contrast, the outcome of ALCL that expresses anaplastic lymphoma kinase (ALK) detected by immunohistochemistry or that bears a t(2;5) by FISH may have a better prognosis when treated with standard CHOP +/- etoposide.

6.2.1 Stage I/II

Treatment: CHOP x 6 cycles + IFRT 30 Gy in 20 fractions

Stage I cutaneous ALCL, ALK positive: RT alone (35 Gy) is appropriate

6.2.2 Stage III/IV

Treatment: CHOP x 6-8 cycles

CHOP-14 + G-CSF x 6-8 cycles
CHOEP x 6-8 cycles (ALK +ve ALCL)

6.3 Mantle cell lymphoma:

- Initial period of observation: asymptomatic, no marrow compromise, no impending organ compromise (see watch and wait criteria for indolent lymphomas)

6.3.1 Limited stage (I, II)

Treatment: CHOP + rituximab x 4 - 6 cycles + involved field RT

6.3.2 Advanced stage (III, IV)

6.3.2.1 Age < 65 years, no comorbidities precluding intensive therapy: plan for autologous stem cell transplantation (ASCT)

Treatment: CHOP + rituximab x 6 cycle
CR, PR: stem cell mobilization , autologous stem cell transplantation

Intensive therapy: chemotherapy +TBI (currently not available at referral center)

Total Body Radiation (TBI)*: 1200 cGy/6 fractions/od/bid days -3, -2, -1, 0
(over 4 days, minimum interfraction interval 6 h). Last fraction in the morning of day 0.

* TBI will be included in the conditioning regimen, for patients age < 60

6.3.2.2 Age > 65, or not considered eligible for ASCT

Treatment: **CVP + rituximab x 6-8 cycles**

6.4 Burkitt Lymphoma:

6.4.1 Low risk/favorable: (stage I-II, normal LDH, only 1 extra-nodal site, ECOG PS 0- 1)

Treatment: **CODOX-M x 3 cycles**

6.4.2 High risk/ unfavorable (stage III/IV, failure to meet criteria for favorable BL)

Treatment: **CODOX-M/IVAC X 2 alternating cycles**

Involved field radiation does not play a role as part of primary therapy for bulky or localized Burkitt lymphoma.

6.5 Extranodal NK lymphoma, nasal type:

Treatment: **Induction CHOP x 1- 2 cycles for symptom control, followed in 2 weeks by IFRT (45 – 50 Gy in 25 fractions over 5 weeks)**, then reassess for continuation of CHOP chemotherapy.

6.6 Indolent Histology Lymphomas

6.6.1 Follicular lymphoma (FL)

Histologies:

Follicular grade 1
Follicular grade 2
Follicular grade 3A
[Follicular grade 3B is managed as diffuse large B cell lymphoma]

6.6.1.1 Stage I/II follicular lymphoma

Treatment: **Involved Field RT 30 Gy in 20 fractions**

For stage I & IIB, IIA extensive, bulk > 5cm, consider combined modality therapy (6 cycles CVP + rituximab) or chemotherapy alone.

For cases treated with complete surgical excision, consider observation as an option.

6.6.1.2 Stage III/IV (FL)

- **Observation**: All patients who present without symptoms and who do not fulfill any requirements for therapy listed below within the first 3 months from diagnosis are candidates for a "watch and wait" approach. Such patients should undergo repeat imaging with CT scans to assess rate of progression of measureable disease; those who do not develop any of the adverse disease characteristics can be followed clinically at regular intervals, until an indication(s) for therapy develops: Table (A.13 a).

BNLI CRITERIA	GELF CRITERIA
1) hematopoietic impairment (Hgb<100g/L, WBC <3.0x109/L, ; Plts<100 g/L), 2) pruritis or B-symptoms, 3) rapidly progressing lymphoma within the last 3 months, 4) life endangering organ involvement, 5) localized bone lesions, 6) renal infiltration 7) macroscopic liver involvement	1) Involvement of 3 nodal sites each with diameter of 3 cm, 2) any nodal or extra-nodal mass 7 cm in diameter, 3) B symptoms, 4) splenomegaly, 5) pleural effusion or ascites, 6) cytopenias: wbc <1.0x109/L or plts <100x109/L 7) leukemic phase of disease with>5.0x109/L

- IFRT for symptom control (total dose 4 Gy in 2 fractions) or local control (total dose 20 – 30 Gy in 5-15 fractions).
- Systemic therapy for symptomatic disease

6.6.2 Marginal zone lymphoma (MZL)

Types:

- Extra-nodal mucosa-associated lymphoid tissue (MALT) lymphoma
- Nodal marginal zone lymphoma
- Splenic marginal zone lymphoma

6.6.2.1 Stage I/II MZL

Stomach: Helicobacter pylori eradication therapy.

For persistent MALT lymphoma despite adequate H. pylori eradication therapy (allow ~ 12 months from eradication therapy):
RT to stomach, perigastric nodes, celiac nodes to 30 Gy in 20 fractions.

Orbit: Involved field RT to 25 Gy in 10-15 fractions.
Other sites: Involved-field RT to 30 Gy in 20 fractions.

For those with disease site and disease extent suitable for complete surgical excision and no residual lymphoma post-surgery, consider observation with no RT (typical sites where this approach is feasible include lung, skin, thyroid, breast).

6.6.2.2 Stage III/IV MZL

Treatment: **R-CVP – 6-8 cycles**
For patients with CR/PR: maintenance rituximab or other alternative induction regimen.

- IF RT for symptom control (total dose 4 Gy in 2 fractions) or local control (total dose 20 – 30 Gy fractionated in 5 – 15 F).

- Patients with splenic marginal zone lymphoma and cytopenias or significant splenomegaly should undergo splenectomy as initial management if fit enough for surgery.

- Patients with SMZL and other marginal zone lymphomas arising in the setting of chronic hepatitis C infection should be considered for initial treatment with ribavirin and interferon as directed by their hepatologist, as complete regression has been reporting following HCV eradication.

7. Radiotherapy protocol:

RT planning process is similar to that in HD.

7.1 External beam planning technique:

7.1.1 *Patient preparation (rectal and bladder status), if abdomen/pelvis in the field.*

- ***The day before simulation***
  - Patient should avoid eating large amount of fruits and vegetables, beans and dairy products.
    - The evening before simulation Patient should take two table spoons of laxative. This will help in bowel movements.
  - The day of simulation
    - Patient should eat light meals before simulation.
    - Avoid large amount of fresh fruits and vegetables, beans and dairy products. If he/she have not had a bowel movement in the past 16 hours, then he/she should take another two table spoons of laxative.
  - One hour before simulation
    - Patient should evacuate the bladder and drink 500 cc of water before simulation to make bladder full (at least 70%). Repeat this bladder filling process before each of daily radiation treatments.

7.1.2 **Immobilization**

- Use of Orfit to relevant site for proper immobilization.
- Knee & Ankle support, Alfa cradle if available will improve immobilization.

7.1.3 Orientation, set-up, marking and reference points

- Patients lie in the comfortable position as per the site to be irradiated.
- A standardized bladder/rectum protocol is used for planning and treatment as mentioned earlier for patients with abdominal/pelvic sites.
- Patient aligned with 3 laser beams. Set 3 marks on the patient skin. The middle one usually in the midline.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points.

7.1.4 Image acquisition

Conventional Simulation

- Conventional simulation is used in selected cases of head & neck & inguinal areas
- Majority of cases are treated with CT based 3D conformal plans.

7.1.5 Target definition:

7.1.5.1 GTV:
Any residual tumor seen clinically or radiologically.

7.1.5.2 CTV:

- The pre chemotherapy imaging is used to define the superior and inferior extent of original disease, which is expanded cranio-caudally by a margin of 1.5 cm. in the direction of potential lymphatic spread. It is not necessary to encompass entire nodal regions or adjacent areas. In the transverse plane, the CTV will include the involved only nodes (or organ) and any residual disease (not the whole pre chemotherapy volume).
- The CTV should not extend into air, muscle planes or bone, unless the lymphoma is invading muscle or bone.
- Direct 3D expansion from the GTV will often need to be extensively edited to constrain the volume with the nodal chain as well as air and tissue planes. In the case of pre-chemotherapy imaging not being available, the patient should be treated using IFRT.

7.1.5.2.1 Supra-diaphragmatic Sites:

These will include:

- Cervical nodes
- Supra-clavicular fossae (SCF).
- Axillae
- Mediastinum and hilum.

7.1.5.2.2 Infra-diaphragmatic sites:

- These will include para-aortic (PA) nodes, mesenteric nodes, spleen and splenic hilum and iliac and inguinal nodes.
- If PA nodes are to be treated with the spleen / splenic hilum, a single volume may be used to encompass all sites.
- If adjacent nodal regions are involved, these may be treated with large fields.

- Alternatively supra and infra diaphragmatic fields may be treated consecutively with a calculated gap between the two and leaving a two to three week interval between treatments.
- Care is needed when matching supra and infra diaphragmatic fields to avoid overlap.

7.1.5.2.3 Extra-Nodal sites: (CTV)

The principles discussed in the nodal lymphoma guidelines will also be applied to irradiation of extra nodal sites. In general, the CTV will include the entire organ affected. Examples of common sites are:

- **Head & Neck:**

Conventionally lymphoma arising in any part of Waldeye's ring will be treated with inclusion of all sites of Waldeye's ring in the radiation field. There is no good evidence of depart from this practice at present, thus whilst a limited GTV may be defined the CTV will include the entire ring from nasopharynx to lingular tonsil. If the disease occurs anywhere in the maxillary antrum, bilateral region will be outlines from base of orbital roof to base of maxillary bone to make the CTV. Parotid lymphomas will be treated using a CTV which includes the entire ipsilateral gland.

- **Stomach & Spleen:**

The entire organ as defined on CT imaging will constitute the CTV. Allowance for organ motion is important in defining the CTV to PTV expansion, in particular cranio-caudally is recommended.

- **Bone**:

Ttraditionally the entire bone has been included in the treatment volume. Where a GTV can be defined then the CTV should include the entire width of a bone and cranio-caudally allow a minimum of 3 cm. margin along the bone marrow cavity.

- **Brain:**

Cerebral lymphoma is characteristically diffuse in nature and the CTV should include the whole brain from base of brain stem to frontal, parietal and occipital lobes.

7.1.5.3 Planning Target Volume: Nodal sites

The CTV will be expanded further to create the PTV to account for organ and set up errors. CTV to PTV margins should be defined individually for each disease site and treatment centre depending upon their technique, set up accuracy and consideration of internal organ motion. Typical margins are as follows:

- Head & Neck – 0.5 to 1 cm. depending on local set up.
- Mediastinum – 1 cm. transversely and 1.5 cm. cranio-caudally.
- All other sites – 1 cm.

7.1.5.4 PTV Extra-Nodal sites:

This will require expansion of the involved node CTV to allow for set up errors and internal organ motion. The same guidelines apply for involved site PTVs. However, particular areas to be aware of are the spleen and stomach, where respiration requires a larger expansion, particularly in the superior and inferior directions (20 mm is recommended). Treatment fields will also include the PTV with a margin for penumbra.

7.1.5.5 OAR CONTOURING:

OAR contouring are different and anatomical site dependant.

7.1.6 Technique:

Three D- Conformal radiotherapy

7.1.7 *Beam arrangement*:

Depends upon the site treated, AP/PA or multiple fields

7.1.8 Beam energies:

6-18 MV depend on the anatomical site and separation

7.1.9 Dose prescription and fractionation.

7.1.9.1 Indolent lymphomas (follicular, small lymphocytic or CLL/SLL) should be given 24 – 30 Gy in 12-15 fractions.

7.1.9.2 Marginal zone lymphoma: Gastric 30 Gy
Other extranodal sites 24-30 Gy
Nodal MZL 24-30 Gy /12-15 F

7.1.9.3 Early mantel 30-36 Gy

7.1.9.4 Palliative local control of SLL, FLL MZL, MCL 2Gy x 2 f which may be repeated as needed

7.1.9.5 Diffuse large BCL:
Consolidation after chemotherapy 30-36 Gy / 20- 24 f
Complementary after PR 40-50 Gy
For 1 ry tretamnent or non candidate for chemotherapy 40-50 Gy

7.1.9.6 All other NHLs should received 30 Gy in 20 fractions. All treatments assume daily fractionation, 1.5 Gy per day, 5 days per week.

7.1.9.7 Boost dose of 6 Gy /4 f can be used in some situation

7.1.9.8 NK-T cell lymphoma
RT as primary treatment 50 65 Gy
RT in combined modality therapy 45-60 Gy

7.1.9.9 Primary cutaneous anaplastic larg cell lymphoma 30-36 Gy

7.1.9.10 Primary cutaneous follicle center or marginal zone lymphoma 24-30 Gy

7.1.9.11 **Dose limitation to OAR.**

Refer to HD protocol

7.1.10 Plan verification and Execution:

- Plan approval should be approved by a senior radiation oncologist in the presence of the concerned physicist and the assigned doctor.
- KV/MV portal images are taken for the first 3 days of treatment then weekly at least.
- These images to be approved by the treating oncologist before attempting subsequent treatment sessions.
- Ideally the treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- In case of suspecious of a major shift, resimulation CT may be done.
- Any systematic errors of more than 3 mm are identified and corrected, and weekly EPIs then taken.
  - The therapist should pay attention on matching of portal images to both the bony landmarks (to confirm same positioning) and to the soft tisse including the airway and the mass if visible (to detect soft tissue variation early especially in case of postoperative radiation where the pneomenectomy side may change and medistinal shift can be marked).
  - Treatments in large patients may show a high random error and then daily portal imaging may be necessary.

7.2. Brachytherapy:

Not applicable.

7.3 Sequelae of treatment

7.3.1 Acute:

acute ***Radiotherapy toxicities are variable according to the irradiated site.*** **It is assessed and scored according to RTOG-EORTC scoring system.**

7.3.2 7.3.2 Late:

- Most important long term toxicities include secondary malignancies (leukaemia, lymphoma and solid tumours) and cardiovascular diseases (coronary artery disease, pericarditis etc).
- Subclinical hypothyroidism.
- Azoospermia in males and ovarian dysfunction in females after pelvic irradiation can occur.

8. Principles of hormonal therapy:

Thyroid replacement therapy may be required for patient who had neck irradiation.

9. Pricnciples ofchemotherapy;

9.1 Diffuse Large B cell lymphoma

9.1.1 Stage I, II

- No risk factors: **R-CHOP x 4 cycles**

- ≥ 1 factor(s): **R-CHOP x 6 cycles**

- Stage I-II testis and epidural presentations should receive CNS prophylaxis: IT methotrexate x 5.

- Patients with primary mediastinal large B cell lymphoma and localized gastric DLBCL should receive involved field radiation following CR or PR following RCHOP, even for presentations that do not meet conventional criteria for bulky disease, based on phase II and cohort data suggesting optimal treatment outcomes with combined modality therapy.

9.1.2 Stage III/IV

R-CHOP x 6-8 cycles (2 beyond CR)

- CT scan after cycle 3 and 6; functional imaging scan (gallium or FDG-PET) for residual imaging abnormalities at end of treatment >2 cm.
- If residual mass post completion of systemic chemotherapy is FDG avid, consider biopsy and salvage chemotherapy and stem cell transplant if biopsy is positive.
- CNS prophylaxis: Some patients with DLBCL are at higher risk of CNS recurrence; the factors that are predictive of such recurrence are controversial but include elevated LDH + > 1 extranodal site; encroachment on or invasion of dura; testicular involvement. For such patients intrathecal chemotherapy (methotrexate +/- cytarabine, hydrocortisone) is suggested for 4-6 treatments.
- Dose-intensity and the use of granulocyte colony-stimulating factor (G-CSF): Evidence currently does not support the use of primary prophylaxis with G-CSF, but such therapy is recommended for patients experiencing febrile neutropenia who have otherwise tolerated full dose R-CHOP. Exceptions to this include patients presenting with bone marrow compromise from lymphoma, elderly patients with significant comorbidities, patients with poor performance status (ECOG >3) and immunocompromised patients (HIV+, organ transplant recipients).
- Six cycles of R-CHOP results in similar PFS and overall survival to 8 cycles with less toxicity; there does not seem to be any advantage to an additional 2 cycles of therapy for those who have achieved PR by CT scan after 6 cycles.
- Patients who are HIV positive and are fit to receive combination chemotherapy should receive 6 cycles of CHOP with antiretroviral therapy and anti-infectious prophylaxis as appropriate for their CD4 counts during treatment.

9.2 Peripheral T cell lymphoma and variants (including Anaplastic Large Cell lymphoma):

9.2.1 Stage I/II

CHOP x 6 cycles

9.2.2 Stage III/IV

CHOP x 6-8 cycles

CHOP-14 + G-CSF x 6-8 cycles
CHOEP x 6-8 cycles (ALK +ve ALCL)

9.3 Mantle cell lymphoma:

9.3.1 Limited stage (I, II)
CHOP + rituximab x 4 - 6 cycles + involved field RT

9.3.2 Advanced stage (III, IV)

9.3.2.1 Age < 65 years, no comorbidities precluding intensive therapy: plan for autologous stem cell transplantation (ASCT)

CHOP + rituximab x 6 cycles
CR, PR: stem cell mobilization , autologous stem cell transplantation

Intensive therapy:

Etoposide 60 mg/kg, i.v., day -4
Melphalan 160 mg/M2, i.v., day -3
Transplant day 0

9.3.2.2 Age > 65, or not considered eligible for ASCT

CVP + rituximab x 6-8 cycles

- Elderly patients with significant co-morbidities or who wish to avoid the toxicity of combination chemotherapy should be treated with chlorambucil 0.1 mg/kg/d for 4-6 months as tolerated.

- **Maintenance/ consolidation therapy**: should be considered for patients with CR or PR after primary therapy (or second-line treatment, if rituximab naïve):
Rituximab 375 mg/m2 weekly x 4 weeks, commencing 3 and 9 months following completion of chemoimmunotherapy.

9.4 Burkitt Lymphoma:

9.4.1 Low risk/favorable: (stage I-II, normal LDH, only 1 extra-nodal site, ECOG PS 0- 1).

CODOX-M x 3 cycles

9.4.2 High risk/ unfavorable (stage III/IV, failure to meet criteria for favorable BL)

CODOX-M/IVAC X 2 alternating cycles

9.4.3 CNS prophylaxis with intrathecal methotrexate and cytarabine is built into both low risk and high risk protocols.

Additional considerations:

- Pre-phase therapy with oral cyclophosphamide and prednisone, along with prophylaxis against tumour lysis (hydration and urinary alkalization, allopurinol) is recommended for patients who are elderly or who present with high disease burden (e.g markedly elevated LDH, stage IV).

- There are no prospective randomized trials evaluating the addition of rituximab to Burkitt lymphoma protocols, but improved outcomes have been reported in retrospective comparisons.

- Patients who are HIV positive and are fit to receive combination chemotherapy should receive CODOX-M/IVAC for two alternating cycles, with antiretroviral therapy and anti-infectious prophylaxis as appropriate based on CD4 counts during treatment.

9.5 Extranodal NK lymphoma, nasal type:

Induction CHOP x 1- 2 cycles for symptom control, then reassess after radiotherapy for continuation of CHOP chemotherapy.

9.6 Indolent Histology Lymphomas

9.6.1 Follicular lymphoma (FL)

9.6.1.1 Stage I/II follicular lymphoma

- For stage I & IIB, IIA extensive, bulk > 5cm, consider combined modality therapy (6 cycles CVP + rituximab) or chemotherapy alone.

9.6.1.2 Stage III/IV (FL)

- Systemic therapy for symptomatic disease

R-CVP – 6-8 cycles
For patients with CR/PR: maintenance rituximab 375 mg/m2 q3mos x 8 doses (2 years).

Alternative induction treatments:

R-CHOP (younger pts, bulky disease) – 6-8 cycles
Oral alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-agent chemotherapy)

9.6.2 Marginal zone lymphoma (MZL)

9.6.2.1 Stage I/II MZL

Stomach: Helicobacter pylori eradication therapy.

For persistent MALT lymphoma despite adequate H. pylori eradication therapy (allow ~ 12 months from eradication therapy):

9.6.2.2 Stage III/IV MZL

R-CVP – 6-8 cycles

For patients with CR/PR: maintenance rituximab 375 mg/m2 q3mos x 8 doses (2 years)

- Alternative induction treatments:
  Fludarabine-containing combinatons (eg. Fludarabine + cyclophosphamide) – 6 cycles.
- Oral alkylator therapy: chlorambucil 0.1 mg/kg/day (for selected patients not appropriate for multi-agent chemotherapy).

For more details about different chemotherapy regimen available for treatment of NHL according to the histologial types, kindly refer to the Medicam oncology department guideline.

10. Managemet of recurrence / relapse:

All cases are discussed in the MDT lymphoma meeting.

10.1 Primary refractory disease: High dose chemotherapy+ stem cell transplantation.

10.2 Relapse: Previous RT (+) 15-20 Gy RT Previous RT (-) 30-40 Gy RT.

10.3 Relapse in stage III-IV cases: Autologous bone marrow transplantation (BMT) or stem cell transplantation.

11. Follow Up

11.1 On Treatment follow up:

- Weekly review in OPD with CBC and for assessment of treatment toxicity.
- Dietary supplements are useful to maintain adequate nutritional needs.
- Some patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological side effects are common.
- A mild increase in dyspnoea or cough is common for patient on mediastinalm irradiation but rarely needs treatment. Intercurrent infections should be excluded.
- Advice on skin care is given.
- When the oesophagus is within the treated volume, pain on swallowing and dysphagia usually begin in the third week of treatment. Systemic analgesia, topical local anaesthetic agents and advice on soft and high calorie diets from a dietician should be available.

11.2 Post completion of treatment follow-up:

First year - Visits every 3 months
2 - 3 years -Visits every 4 months
4 - 5 years -Visits every 6 months
> 5 years - annual follow up

In general, alternate follow up visits between attending medical Oncologist/hematologist and radiation oncologist. Family physicians are encouraged to participate in the follow up as outlined, particularly for visits beyond 5 years from treatment.

12. Ongoing departmental studies:

Not applicable

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