

STANDARD TREATMENT GUIDELINES ONCOLOGY

**Ministry of Health & Family Welfare
Govt. of India**

Group Head Coordinator of Development Team

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NAME OF CONDITION: BILIARY CANCER

I. WHEN TO SUSPECT/ RECOGNIZE?

a) Introduction:

Bile duct cancer is a relatively uncommon cancer with annual incidence of 1-2/100,000 in Western studies. Recent trends show increasing incidence probably due to better diagnostic techniques. Although biliary cancer can occur anywhere in the biliary tract, 40-60% of them involve the hilum. 90% of these tumors are well differentiated and mucin producing adenocarcinomas. The peak age for bile duct cancer is in the seventh decade and more males are affected than females. Patients usually presented with progressive jaundice, itching and weight loss.

b) Case definition:

For both situations of care (*mentioned below**)

INCIDENCE OF THE CONDITION IN OUR COUNTRY

Worldwide incidence of biliary cancer is about 0.01% - 0.2% in large autopsy series. However the Indian data is still awaited. Majority of the patients are elderly males over sixty years.

II. DIFFERENTIAL DIAGNOSIS

Majority of the patients with a hilar stricture harbor malignancy. However an alternate diagnosis is possible in 10-15% of patients.

The differential diagnoses should consider gall bladder carcinoma, Mirizzi's syndrome and Idiopathic benign focal stenosis of the bile duct.

III. PREVENTION AND COUNSELING

Most of the cases occur sporadically and a clear cut etiological agent is not indicated in biliary tract malignancy. However, a high incidence is noted in patients with congenital biliary cystic disease (15-20%). A diagnosis of such a condition should warrant surgical treatment, so as to prevent the development of biliary malignancy in future. However, the benefit of surgery done after 20 yrs of age is questionable.

Stringent measures of radiation protection is to be offered to the workers in the nuclear energy sector, since radioisotopes used commercially like Thorium, Radon etc are thought to be associated with the development of cholangiocarcinoma.

IV. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

The early symptoms of cholangiocarcinoma are non specific. Anorexia weight loss and pruritus are most common. 90% of the patients come to attention with painless jaundice. Clinical examination reveals jaundice and may also find enlarged firm liver.

Diagnostic criteria

Abdominal ultrasound examination which reveals dilated intrahepatic biliary radicles with a collapsed gall bladder and extrahepatic bile duct must be suspected to be a case of hilar obstruction unless proven otherwise. Possible differential diagnosis of gall bladder cancer or Mirizzi syndrome must be considered, and further evaluation must be carried out by a contrast enhanced CT scan or MRI, and the expertise of a tertiary care center taken at this stage.

Diagnosis is based on radiological criteria and pathological confirmation is not mandatory prior to surgery in resectable lesions. Histopathological proof can only be achieved by endoscopic brush cytology or EUS guided needle biopsy and is not recommended prior to resection when the lesion is deemed resectable.

Histological confirmation is mandatory prior to chemotherapy or radiotherapy.

Investigations:

MDCT can give valuable information regarding the level of obstruction, vascular invasion, and presence of atrophy/hypertrophy complex of liver lobes.

MRCP is the investigation of choice for obtaining a cholangiogram.

ERCP or PTC allows bile sampling for cytology, which is positive in about 30% of cases. Combined brush cytology and biopsy specimens increase yield to 40–70%.

Negative cytology from brushings does not exclude malignancy.

Treatment:

Prior radiological evaluation of resectability and patient's performance status determine the treatment.

In Resectable hilar cholangiocarcinoma standard curative surgery entails hemihepatectomy with caudate lobectomy and extrahepatic bile duct excision with regional lymphadenectomy.

Aggressive resections with combined portal vein resection to achieve RO resection may be considered in selected cases.

Preoperative Biliary drainage may salvage segments of hepatic parenchyma and reduce risk of postoperative liver failure.

Portal vein embolization to increase the remnant liver volume in patients with post-resection volumes are less than 25%.

Role of adjuvant therapy after resection remains controversial; however chemotherapy or chemo radiation may be tried

Unresectable tumors require endoscopic or percutaneous biliary drainage or stenting. Surgical bilio-enteric bypass may be required. Palliative Gemcitabine based chemotherapy may be considered along with supportive care.

Liver transplantation is indicated at selected centres, for patients with early stage cholangiocarcinoma and anatomically unresectable lesions, but this approach should not be offered outside the scope of clinical trials.

***Situation 1: At Secondary Hospital/ Non-Metro situation: Optimal Standards of Treatment in Situations where technology and resources are limited**

a) Clinical Diagnosis

Cholangiocarcinoma is to be suspected in an elderly patient with symptoms of pruritus ,painless and progressive jaundice.

b) Investigations:

MDCT
MRCP

c) Treatment:

Biliary drainage and supportive care with or without chemoradiotherapy for unresectable and metastatic disease. This condition is not however suitable for treatment at a secondary hospital, and must be referred to a tertiary care center.

Standard Operating procedure

- a. In Patient**
- b. Out Patient**
- c. Day Care**

d) Referral criteria:

Biliary obstruction with undilated gall bladder or extrahepatic bile ducts must be regarded as hilar obstruction unless proven otherwise. These patients must be referred for evaluation and management to a tertiary care center.

Patients requiring major liver resections resection or portal vein resection.

***Situation 2: At Super Specialty Facility in Metro location where higher-end technology is available**

a) Clinical Diagnosis:

Cholangiocarcinoma is to be suspected in an elderly patient with symptoms of pruritus ,painless and progressive jaundice.

b) Investigations:

MDCT, MRCP
EUS, Endoscopic/Percutaneous cholangioscopy,

c) Treatment:

Hepatectomy with caudate lobectomy and excision of the extrahepatic Biliary tree with regional lymphadenectomy in resectable disease.

Extended resections with portal vein resection and reconstruction where portal vein is involved.

Biliary drainage and supportive care with or without chemoradiotherapy for unresectable and metastatic disease.

Standard Operating procedure

- a. In Patient**
- b. Out Patient**
- c. Day Care**

d) Referral criteria:

Patients considered candidates for liver transplantation may be referred to transplant units.

V. *WHO DOES WHAT? and TIMELINES*

- a. Doctor***
- b. Nurse***
- c. Technician***

VI. FURTHER READING / REFERENCES

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RESOURCES REQUIRED FOR ONE PATIENT / PROCEDURE (PATIENT WEIGHT 60 KGS)

(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

Situation	HUMAN RESOURCES	INVESTIGATIONS	DRUGS & CONSUMABLES	EQUIPMENT
1				
2				

NAME OF CONDITION: Breast Cancer

I. WHEN TO SUSPECT/ RECOGNIZE?

Introduction:

Breast cancer is the commonest cancer among women worldwide. In recent years, breast cancer has emerged as the commonest female malignancy in the majority of Asian countries. In India, breast cancer incidence has overtaken cervical cancer incidence in most urban registries. (1) This is attributed to several factors including diet, lifestyle, lowered fertility with increasing age at first childbirth, obesity etc.

Case definition:

For both situations of care (*mentioned below**)

Histopathologically or cytopathological diagnosis of invasive or non invasive cancer of tissue obtained from breast.

II. INCIDENCE OF THE CONDITION IN OUR COUNTRY

According to Globocan 2008, with an estimated 1.38 million new breast cancer cases diagnosed each year, female breast cancer is the second most common cancer in the world and the most common cancer among women, accounting for 4,58,000 cancer deaths per year. (2) In India, breast cancer incidence varies from urban (30 per 100,000 population per year) to rural (5 per 100000 population per year) areas. (1)

III. DIFFERENTIAL DIAGNOSIS

Mammary dysplasia (fibrocystic condition of the breast), fibroadenoma, intraductal papilloma, lipoma, fat necrosis, cystosarcoma phylloides, breast abscess and others depending on the clinical context.

IV. PREVENTION AND COUNSELING

Factors Associated With Increased Risk of Breast Cancer

1. Hormone replacement therapy
2. Obesity
3. Lack of exercise
4. Later age at first child birth
5. Lack of Breast-feeding
6. Family history of breast and ovarian cancers

A lactational period of 6 months or more is associated with decreased risk of breast cancer.

Similarly, having the first live birth after age 30 doubles the risk compared to having first live birth at age less than 25 years. (3) Gaining weight after menopause can increase a woman's risk. A recent study found that putting on 9.9 kg (22 lbs) after menopause increases the risk of developing breast cancer by 18%. (4) Hormone replacement therapy used by women attaining menopause has also been associated with increased risk of breast cancer. (5)

While the societal trend towards reduced fertility is clearly non-modifiable it is possible to educate young Indians about the appropriate age to initiate childbearing (perhaps best before the age of 30 years) and the importance of breast feeding, not only for the child but also the woman. Obesity is the other potentially modifiable risk factor that requires

multidimensional preventive attention with major health benefits that extend beyond cancer prevention. Societal and public health intervention in these areas has the potential to abrogate much of the increase in breast cancer incidence that has been observed in the West.

V. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

A number of international guidelines exist in order to ensure uniformity and quality in the delivery of care to patients with breast cancer. (6-9) The majority of guidelines have been developed in the context of evidence and clinical practice in the Western world. There is little representation from developing countries, if any, in the expert panels that formulate these guidelines. Clinical practice in developing countries, however, continues to be largely guided by these guidelines since they are based on high quality evidence with expert appraisal. Many of these guidelines are not literally applicable to developing countries because of constraints on resources and/or expertise.

***Situation 1: At Secondary Hospital/ Non-Metro situation: Optimal Standards of Treatment in Situations where technology and resources are limited**

a. Clinical Diagnosis:

Pathology guidelines:

- Histopathological diagnosis of breast cancer by a biopsy (prior to neoadjuvant chemotherapy, if planned) or on the surgical specimen is a must. In the latter situation

in operable breast cancer, pre-operative establishment of diagnosis by fine needle aspiration is appropriate and acceptable.

- The essential elements of a histopathological report include the subtype, grade, adequacy of margins, axillary nodal status and immunohistochemically determined ER, PgR and CerbB2 (HER2)

Immunohistochemistry (IHC) facility not mandatory in all centres that treat breast cancer, but referral affiliation with a central laboratory for obtaining this information in all patients is mandatory. The ASCO/CAP guidelines should be followed for reporting on breast cancer specimens. (10, 11) ER and PR are important for prognostication and hormonal therapy of breast cancer. HER2 is important for guiding the choice of systemic HER2 targeted therapy in primary breast cancer, if the latter is feasible. Knowledge of HER2 status also has some prognostic value and predictive capability for anthracycline benefit. [5, 6, 7, 12]

b. Investigations:

Radiology guidelines

All centres treating breast cancer should have facilities for plain chest radiograph and ultrasound scanning of the abdomen. However, such centres need not necessarily have facilities for breast imaging including mammography, breast sonography and other advanced imaging techniques. Mastectomy is an appropriate surgical modality in such centres. Standard staging in locally advanced breast cancer includes chest radiograph or

CT scan of chest, USG Abdomen or CECT abdomen, and bone scan. Metastatic workup is not required in clinically early stage breast cancer.

c. Treatment:

Surgical guidelines

Modified radical mastectomy (MRM) with axillary clearance is an appropriate surgical option for all stages of operable breast cancer and those who become operable after neoadjuvant treatment. The long-term safety and quality of life gains with breast conserving surgery have been proven in high quality studies and this procedure should be offered to patients who are eligible to receive it. Thus eligible and desirous patients should be referred to an appropriate higher centre for breast conservation.

A modified radical mastectomy involves removal of the entire involved breast using an elliptical skin incision, including the skin overlying the tumor and the nipple-areola complex with the underlying pectoralis fascia, sparing both the pectoralis muscles, along with the removal of at least levels I and II axillary lymph nodes. Level III axillary lymph nodes should always be excised in large tumors, node positive axilla and locally advanced breast cancers post neoadjuvant chemotherapy.

1. Surgery after Neoadjuvant chemotherapy (NACT)

The standard surgery for patients with LABC after NACT is MRM.

2. Full axillary dissection is the standard of care

A full axillary clearance that includes level III lymph nodes be undertaken as a standard procedure in breast cancer surgery in developing countries. There is relative abundance of large, non-screen detected cancers and locally advanced breast cancers in these regions with high possibility of axillary nodal involvement. (13) It needs to be noted that extensive axillary procedures could lead to increased incidence of adverse effects like shoulder stiffness and arm edema. (14)

3. Depot hydroxyprogesterone prior to surgery for primary breast cancer

The adoption of pre-operative injection depot hydroxyprogesterone as a standard of care in patients with operable breast cancer is not currently ready for routine practice. There is a recent large randomised trial and other reports suggesting a positive benefit in node positive and large tumours but replication these findings is needed. (15)

Radiation therapy guidelines:

1. Use of post mastectomy radiation

Post Mastectomy radiation should be used in all patients with >5 cm pathological tumour size and/or 4 or more positive nodes in axilla. (16)

2. Use of radiation in patients with 1-3 positive axillary nodes after mastectomy

Among post mastectomy patients with 1-3 positive nodes, patients with additional poor risk features (young age, vessel invasion, inadequate axillary lymph node dissection) should receive radiotherapy. A subgroup analysis from the Danish study that showed a survival benefit in these (1-3 node positive) patients equivalent to those with more than

3 involved nodes involved and other studies which have tried to analyse specific risk factors in these patients. (17, 18)

3. Use of appropriate megavoltage machines for radiation therapy may be used.

Linear accelerator or Cobalt⁶⁰ (Co⁶⁰) unit is a valid option for radiotherapy after mastectomy when such treatment is indicated. [19]

4. Use of axillary nodal radiation after surgery.

There is no routine indication of using axillary nodal irradiation after adequate surgical clearance. [20] Such radiation can be used in rare instances in patients with microscopic or gross residual cancer in the axilla after surgical dissection.

Systemic Therapy in Breast Cancer

The following suggestions are a framework of suggestions in order to ensure optimal delivery of care to the majority of breast cancer patients presenting to all levels of the healthcare system in India. The panel recognizes that departures from guidelines may be required in individual cases in response to the specifics.

- I. Adjuvant chemotherapy

Adjuvant chemotherapy has become an important component of breast cancer management in the last 30 years. Robust evidence for its use has been generated in successive reviews of individual patient data by the Early Breast Cancer Trialists Cooperative Group. [21]

- a. Chemotherapy after surgery may be omitted in the following group of patients who may not benefit from the use of adjuvant chemotherapy. Such patients

could receive adjuvant hormone therapy alone. Adjuvant chemotherapy should be considered in all other patients who have no contra-indications to its use.

- i. Low grade tumors with strong estrogen and progesterone receptor positivity, without lympho vascular space invasion which are $\leq 2\text{cm}$ and node negative in post menopausal women. [8]

1. Optimal Adjuvant chemotherapy

Anthracycline based chemotherapy is the backbone of adjuvant chemotherapy[21]

- In node negative early breast cancer patients 6 cycles of anthracycline based chemotherapy should be used.
- In those with positive lymph nodes or locally advanced breast cancer, anthracycline and taxane based chemotherapy given sequentially is preferred. [22, 23]. If taxane based chemotherapy is not feasible or contraindicated, 6 cycles of anthracycline based chemotherapy is an acceptable alternative
- CMF chemotherapy may be considered as an acceptable alternative when anthracycline based chemotherapy is not possible due to feasibility issues or contra-indications.
- Ovarian ablation (surgical or radiation) may be considered in certain patients, in hormone receptor positive patients.

2. Chemotherapy for LABC

Neoadjuvant chemotherapy is given with the primary aim of making inoperable tumors operable in locally advanced breast cancer

- The optimal number of chemotherapy cycles is usually 3 to 6 cycles of neoadjuvant chemotherapy. [24, 25]
- Anthracycline and taxane based chemotherapy is preferred. [26, 27] Sandwich therapy (chemotherapy followed by surgery followed by more chemotherapy) is widely practiced and is appropriate. Anthracycline based chemotherapy alone may also be used when taxane based chemotherapy not possible or contraindicated.
- In HER 2 positive patients trastuzumab may be added to chemotherapy in the neoadjuvant setting, if feasible. [28, 29] Despite randomized evidence indicating its cardiac safety in the neoadjuvant setting, concomitant use of anthracyclines and trastuzumab is not widely practiced. Taxanes (paclitaxel or docetaxel) are the preferred concomitant partner for trastuzumab.
- Neoadjuvant hormone therapy may be considered in post menopausal women with strong hormone receptor positivity. [30] Aromatase inhibitors are preferred over tamoxifen in this setting. [31, 32] The optimal duration of treatment is not well defined but may vary from 4-8 months or until after best response. [33]

II. Adjuvant Hormonal Therapy

Adjuvant hormonal therapy significantly improves survival in both pre and post menopausal women expressing hormone receptors. [21] It should be given to all patients expressing any degree of estrogen and or progesterone receptor positivity. The optimal duration of hormone therapy is 5 years. [8]

- Premenopausal women should receive tamoxifen for 5 years.[8] Addition of ovarian suppression to tamoxifen till now not proven to be of additional benefit.
- Post menopausal women aromatase inhibitors is preferred either for 5 years or as switch therapy with 2-3 years of tamoxifen. [34, 35]
- Tamoxifen for 5 years in post menopausal women is an acceptable alternative to aromatase inhibitors. [21]

III. Adjuvant Targeted Therapy

Adjuvant targeted therapy is currently recommended with trastuzumab in patients with HER2 positive disease either after completion of chemotherapy or starting with the taxane component of the chemotherapy regimen. This is based on the proven benefits of adjuvant trastuzumab in disease-free and overall survival. American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines suggest the criteria of >30% intense and complete staining (IHC) or FISH amplification >2.2 for HER2 positivity. [11] The present standard is to give trastuzumab for 1 year. [36, 37] There is also some evidence for the benefit of shorter duration (9-12 weeks) of adjuvant trastuzumab therapy and this an acceptable alternative in view of its wider financial feasibility. [38] When not feasible , the use of chemotherapy (preferable anthracycline based) without trasztuzumab is an acceptable alternative in patients with HER 2 overexpressing tumours.

Patients should be routinely screened for cardiac contraindications to trastuzumab before starting this therapy and the cardiac function should be routinely monitored every 3-4 months using echocardiography or MUGA scan during this treatment.

Follow-up of patients after primary treatment:

1. Need for follow-up after primary treatment.

At present regular post-treatment follow up of all patients with primary breast cancer should be considered. It is however notable that there is lack of evidence from randomized trials supporting any particular follow-up sequence or protocol. [39, 40]

2. Use of investigative modalities during follow-up.

An annual to biennial mammogram is the only routinely required investigation during follow-up in patients who are asymptomatic and have normal physical examination. This is based on evidence from two randomized trials that failed to prove any benefit from more extensive investigations of asymptomatic patients during follow up care. [41, 42]

Standard Operating procedure: Not applicable

VII. Referral criteria:

Patients should be referred to a higher center (or another center) in the following situations.

- a) The facility of treatment is not available at the treating center – e.g. breast conservation, advanced radiation delivery techniques if necessary, diagnostic dilemmas etc.
- b) The waiting list of patients for a particular treatment or therapy is excessively long (please see the time frames stated in this document)

***Situation 2: At Super Specialty Facility in Metro location where higher-end technology is available**

a) Clinical Diagnosis:

Pathology guidelines:

1. Histopathological diagnosis of breast cancer by a biopsy (prior to neoadjuvant chemotherapy, if planned) or on the surgical specimen is a must. In the latter situation in operable breast cancer, pre-operative establishment of diagnosis by fine needle aspiration is appropriate and acceptable.
2. The essential elements of a histopathological report include the subtype, grade, adequacy of margins, axillary nodal status and immunohistochemically determined ER, PgR and CerbB2 (HER2).

Immunohistochemistry (IHC) facility for determination of ER, PR and HER2 should be available. Fluorescent in situ hybridization (FISH) for HER2 amplification should also be available at tertiary hospitals. The ASCO/CAP guidelines should be followed for reporting. [10, 11] ER and PR are important for prognostication and hormonal therapy of breast cancer. HER2 is important for guiding the choice of systemic HER2 targeted therapy in primary breast cancer, if the latter is feasible. There is also some prognostic and predictive capability (for anthracycline benefit) of HER2 testing. [12] In cases with equivocal (2+) HER2 score on IHC, fluorescent in situ hybridization (FISH) should be done.

[11]

3. Incorporation of multigene assays in clinical decision making:

With the available evidence and lack of validation in prospective randomized trials versus conventional decision-making, routine incorporation of multigene assays like

Recurrence Score (RS, Oncotype DX™) in clinical decision making including prognostication and prediction of chemotherapy benefit is not standard. [43]

VIII. Investigations:

Radiology guidelines

These centers should have facilities for mammography, local breast sonography and other advanced imaging techniques (CT scan, radionuclide bone scan etc). Magnetic resonance imaging (MRI) of the breast and positron emission tomography (PET) scans are being increasingly used in the management of breast cancers. While there may be specific clinical situations that justify the use of these techniques, their routine use in the management of breast cancer is not recommended due to lack of robust evidence of benefit.

1. Local imaging prior to surgery

Routine use of mammography and/or breast ultrasound in the evaluation of cases with early stage operable breast cancer should be considered in order to facilitate surgical decisions. Addition of diagnostic breast ultrasound to mammography increases the accuracy and diagnostic yield, especially in patients with dense breasts and asymmetric densities, in addition to providing image guidance for diagnostic procedures such as biopsies. [44]

2. Routine breast MRI prior to breast conserving surgery

Routine use of breast MRI prior to BCT is not recommended. Evidence from randomized trial evidence has revealed a lack of benefit from routine preoperative breast MRI and has also suggested a high rate of false positives with this technique. [45]

3. Staging for locally advanced breast cancer

Standard staging in locally advanced breast cancer includes chest radiograph or CT scan of chest, ultrasound or CT scan of the abdomen and bone scan. Metastatic workup is not routinely required in clinically early stage breast cancer.

4. PET-CT for routine staging in early and locally advanced breast cancer

Routine use of PET or PET-CT scanning for pre- treatment staging assessment of patients with early or locally advanced breast cancer is not recommended. [46]

b) Treatment:

1. Mastectomy with axillary clearance in breast cancer.

Modified radical mastectomy (MRM) with axillary clearance is an appropriate surgical option for all stages of operable breast cancer and those who become operable after neoadjuvant treatment. A modified radical mastectomy involves removal of the entire involved breast using an elliptical skin incision, including the skin overlying the tumor and the nipple-areola complex with the underlying pectoralis fascia, sparing both the pectoralis muscles, along with the removal of at least levels I and II axillary lymph nodes. Level III axillary lymph nodes should always be excised in large tumors, node positive axilla and locally advanced breast cancers post neoadjuvant chemotherapy.'

2. Use of breast conservation therapy (BCT) in developing countries

Breast conserving surgery should be considered for all eligible patients in developing countries. There is overwhelming evidence for the equivalent safety and efficacy of BCT compared to mastectomy in appropriately selected patients. [47, 48] Tumors in developing parts of the world are most often not screen detected, larger, and there is variable availability of expertise for undertaking breast conservation [49]. Such patients should be referred from secondary to tertiary centers with available expertise and infrastructure for breast conservation. Communication of the axillary dissection with the breast cavity should be avoided as far as possible. Separate incisions prevent transfer of seroma fluid between the lumpectomy and axillary areas and improve the cosmetic outcome. [22]

3. Use of oncoplastic procedures

Oncoplastic procedures should be performed only in specialized centres with multidisciplinary expertise in these techniques. [50]

4. Defining adequacy of margins in primary breast surgery

Margins after BCT should be technically free. Guidelines have variously defined an adequate margin in breast conservation from 1mm to 10 mm or more. [51, 52]

Interestingly, the rate of finding IDC in the revised specimens has been in the range of only 30-40%. [53] Although there are conflicting reports, it is evident that obtaining a clean negative margin is desirable.

5. Surgery after neoadjuvant chemotherapy (NACT)

The standard surgery for patients with LABC is MRM after NACT. [54] In selected patients, BCT can be considered. The initial location and extent of tumor should be marked using techniques like biopsy scar, clips, tattoos etc. in patients being planned for NACT. This facilitates ease of subsequent surgery and has a bearing on local control. [55, 56] It should be noted that breast conservation is a valid option in selected cases of large or locally advanced breast cancer who achieve excellent response after NACT. [57, 58] Expert judgment should be applied during the use of this procedure in patients with large and locally advanced breast cancer.

6. Full axillary dissection as a routine standard of care

A full axillary clearance that includes level III lymph nodes should be undertaken as a standard procedure in breast cancer surgery in developing countries. There is relative abundance of large, non-screen detected cancers and locally advanced breast cancers in these regions with high possibility of axillary nodal involvement. [49] However, it needs to be noted that extensive axillary procedures could lead to increased incidence of adverse effects like shoulder stiffness and arm edema. [59]

7. Sentinel lymph node procedure and other axillary sampling in breast cancer patients

Sentinel lymph node biopsy (SLNB) could be considered in carefully selected patients with early breast cancer in clinically negative axilla in centres that have this expertise. [60, 61] SLNB is not routinely recommended in lieu of formal axillary dissection view of higher degree of nodal positivity in this country. However, centres who have standardized this procedure in their institutions with documented results and less than 5-10% false negative rates, may consider this option in highly selected patients with

early breast cancer. Anatomically defined sampling of lower level axillary lymph nodes could also be considered an alternative form of reduced axillary surgery in centres with this expertise and with the same caveats as for SLNB. [62, 63]

8. Depot hydroxyprogesterone prior to surgery for primary breast cancer

The adoption of pre-operative injection depot hydroxyprogesterone as a standard of care in patients with operable breast cancer is not recommended. There is a recent large randomised trial and other reports suggesting a benefit in node positive tumours but replication of these findings in other studies is needed for routine care recommendation. [15, 64, 65, 66]

Radiation therapy guidelines:

1. Use of post mastectomy radiation

Post Mastectomy radiation should be used in all patients with >5 cm pathological tumor size and/or 4 or more positive nodes in axilla. [16]

2. Use of radiation in patients with 1-3 positive axillary nodes after mastectomy

Among post mastectomy patients with 1-3 positive nodes, patients with additional poor risk features (young age, vessel invasion, inadequate axillary lymph node dissection) should receive radiotherapy. A subgroup analysis from the Danish study that showed a survival benefit in these (1-3 node positive) patients equivalent to those with more than 3 involved nodes involved and other studies which have tried to analyse specific risk factors in these patients. [17, 18]

3. Use of radiotherapy after breast conservation

Radiotherapy to the entire breast should be given to all patients with breast conservation. Whole breast radiotherapy should be followed by boost to the tumour bed by any suitable technique available at the center.

4. Use of appropriate megavoltage machines for radiation therapy may be used.

Linear accelerator or Cobalt⁶⁰ (Co⁶⁰) unit are valid options for radiotherapy after mastectomy when such treatment is indicated. (19)

5. Use of tumor bed boost after BCT.

Tumour bed boost should be given to all patients after whole breast radiotherapy, based on randomized evidence that its use improves local failure rates. [67, 68] Since no boost technique has been shown to be better than others (69), any reasonable locally available technique could be used. A higher boost dose is unlikely to compensate for the deleterious effect of a positive margin.

6. Use of axillary nodal radiation after surgery.

Use of axillary nodal irradiation after adequate surgical clearance is not routinely recommended. [20] Such radiation can be used in rare instances in patients with microscopic or gross residual cancer in the axilla after surgery.

7. Use of accelerated partial breast radiation (APBI).

APBI should be considered in a highly selected group of patients with low risk features (such as age > 65 years, pathological tumour size < 2cm, and negative axillary nodes) which is consistent with the recent ASTRO guidelines. [70] There has been recent

interest in using brachytherapy as the sole modality of radiation to decrease the treatment time and toxicities without compromising control. [71, 72]

Systemic Therapy Guidelines

The following suggestions are a framework of suggestions in order to ensure optimal delivery of care to the majority of breast cancer patients presenting to all levels of the healthcare system in India. The panel recognizes that departures from guidelines may be required in individual cases in response to the specifics.

IV. Adjuvant chemotherapy

Adjuvant chemotherapy has become an important component of breast cancer management in the last 30 years. Robust evidence for its use has been generated in successive reviews of individual patient data by the Early Breast Cancer Trialists Cooperative Group. [21]

- a. Chemotherapy after surgery may be omitted in the following group of patients who may not benefit from the use of adjuvant chemotherapy. Such patients could receive adjuvant hormone therapy alone. Adjuvant chemotherapy should be considered in all other patients who have no contra-indications to its use.
 - i. Low grade tumors with strong estrogen and progesterone receptor positivity, without lympho vascular space invasion which are ≤ 2 cm and node negative in post menopausal women. [8]

3. Optimal Adjuvant chemotherapy

Anthracycline based chemotherapy is the backbone of adjuvant chemotherapy [21]

- In node negative early breast cancer patients 6 cycles of anthracycline based chemotherapy should be used.
- In those with positive lymph nodes or locally advanced breast cancer, anthracycline and taxane based chemotherapy given sequentially is preferred. [22, 23]. If taxane based chemotherapy is not feasible or contraindicated, 6 cycles of anthracycline based chemotherapy is an acceptable alternative
- CMF chemotherapy may be considered as an acceptable alternative when anthracycline based chemotherapy is not possible due to feasibility issues or contraindications.
- Ovarian ablation (surgical or radiation) may be considered in certain patients, in hormone receptor positive patients.

4. Chemotherapy for LABC

Neoadjuvant chemotherapy is given with the primary aim of making inoperable tumors operable in locally advanced breast cancer

- The optimal number of chemotherapy cycles is usually 3 to 6 cycles of neoadjuvant chemotherapy. [24, 25]
- Anthracycline and taxane based chemotherapy is preferred. [26, 27] Sandwich therapy (chemotherapy followed by surgery followed by more chemotherapy) is widely practiced and is appropriate. Anthracycline based chemotherapy alone may also be used when taxane based chemotherapy not possible or contraindicated.

- In HER 2 positive patients trastuzumab may be added to chemotherapy in the neoadjuvant setting, if feasible. [28, 29] Despite randomized evidence indicating its cardiac safety in the neoadjuvant setting, concomitant use of anthracyclines and trastuzumab is not widely practiced. Taxanes (paclitaxel or docetaxel) are the preferred concomitant partner for trastuzumab.
- Neoadjuvant hormone therapy may be considered in post menopausal women with strong hormone receptor positivity. [30] Aromatase inhibitors are preferred over tamoxifen in this setting. [31, 32] The optimal duration of treatment is not well defined but may vary from 4-8 months or until after best response. [33]

V. Adjuvant Hormonal Therapy

Adjuvant hormonal therapy significantly improves survival in both pre and post menopausal women expressing hormone receptors. [21] It should be given to all patients expressing any degree of estrogen and or progesterone receptor positivity. The optimal duration of hormone therapy is 5 years. [8]

- Premenopausal women should receive tamoxifen for 5 years.[8] Addition of ovarian suppression to tamoxifen till now not proven to be of additional benefit.
- Post menopausal women aromatase inhibitors is preferred either for 5 years or as switch therapy with 2-3 years of tamoxifen. [34, 35]
- Tamoxifen for 5 years in post menopausal women is an acceptable alternative to aromatase inhibitors. [21]

VI. Adjuvant Targeted Therapy

Adjuvant targeted therapy is currently recommended with trastuzumab in patients with HER2 positive disease either after completion of chemotherapy or starting with the taxane component of the chemotherapy regimen. This is based on the proven benefits of adjuvant trastuzumab in disease-free and overall survival. American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines suggest the criteria of >30% intense and complete staining (IHC) or FISH amplification >2.2 for HER2 positivity. [11] The present standard is to give trastuzumab for 1 year. [36, 37] There is also some evidence for the benefit of shorter duration (9-12 weeks) of adjuvant trastuzumab therapy and this an acceptable alternative in view of its wider financial feasibility. [38] When not feasible, the use of chemotherapy (preferable anthracycline based) without trastuzumab is an acceptable alternative in patients with HER 2 overexpressing tumours.

Patients should be routinely screened for cardiac contraindications to trastuzumab before starting this therapy and the cardiac function should be routinely monitored every 3-4 months using echocardiography or MUGA scan during this treatment.

Follow-up of patients after primary treatment:

1. Need for follow-up after primary treatment.

At present regular post-treatment follow up of all patients with primary breast cancer should be considered. It is however notable that there is lack of evidence from randomized trials supporting any particular follow-up sequence or protocol. [39, 40]

2. Use of investigative modalities during follow-up.

An annual to biennial mammogram is the only routinely required investigation during follow-up in patients who are asymptomatic and have normal physical examination. This

is based on evidence from two randomized trials that failed to prove any benefit from more extensive investigations of asymptomatic patients during follow up care. [41, 42]

Standard Operating procedure: Not Applicable

- a. In Patient**
- b. Out Patient**
- c. Day Care**

c) Referral criteria:

Patients should be referred to a higher center (or another center) in the following situations.

1. The facility of treatment is not available at the treating center – e.g. breast conservation, advanced radiation delivery techniques if necessary, diagnostic dilemmas etc.
2. The waiting list of patients for a particular treatment or therapy is excessively long (please see the time frames stated in this document)

VI. WHO DOES WHAT? and TIMELINES

a. Doctor

Doctor is the team leader in the entire set up. In the context of breast cancers the doctors would include specialists from Medical Oncology, Radiation Oncology, Surgical Oncology, pathology , radiology and other allied specialities. A joint clinic (tumour board) for taking collective decisions regarding the patients should be preferred.

Suggested timelines

Surgery

Date of registration to surgery: 3 weeks

Date of Joint Clinic to surgery: one week

Chemotherapy

Surgery to 1st cycle of chemo: 4 weeks

1st cycle to 6th cycle: 120 days

1st cycle to 8th cycle: 160 days

Radiotherapy

Surgery to 1st fraction of radiotherapy 200 days

b. Nurse: NA

c. Technician: NA

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RESOURCES REQUIRED FOR ONE PATIENT / PROCEDURE (PATIENT WEIGHT 60 KGS)

(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

Situation	HUMAN RESOURCES	INVESTIGATIONS	DRUGS & CONSUMABLES	EQUIPMENT
1				
2				

Chronic Cancer Pain Management Guidelines:

These guidelines are meant for management of patients with the following pain scenarios:

- 1) Patients reporting with moderate to severe pain prior to any cancer therapy
- 2) Patients with advanced disease (including residual or recurrent disease)
- 3) Patients requiring pain relief during the cancer therapy esp. during chemotherapy or radiotherapy
- 4) Patient at end of life
- 5) Pain in cancer survivors.

ETIOPATHOLOGY OF PAIN

- Pain can be somatic or visceral or neuropathic in origin. It can either be caused by the disease itself or by cancer therapy or may be unrelated to cancer.
- The pain assessment is largely multidimensional.
- It includes
 - The physiological component (nociception);
 - The sensory component (i.e. the subject's perception of nociception, such as pain location, intensity and quality).
 - The affective component (i.e. mood & anxiety response)
 - Cognitive component (i.e. how the pain affects patients' thought processes and how the patients view themselves),
 - Behavioral components (i.e. pain behaviors such as analgesic intake or activity level) are assessed during a comprehensive patient assessment.

I. Cancer Pain Assessment Protocol

1. Aim:
To lay down guidelines for
 - a. Comprehensive assessment of patients with cancer for all types of pain
 - b. Appropriate treatment regimens based on the underlying mechanisms causing pain.

2. Scope of these guidelines
 - a. Help clinicians assess and manage cancer pain effectively
 - b. To minimize risk of side effects due to analgesics
 - c. To standardize prescriptions and procedures
 - d. To individualize treatment with the goal of maximizing function & quality of life

3. Assessment of Pain

3.1 Who should assess patient's pain?

The patient himself/herself is the most reliable assessor of pain and should, where possible, be the prime assessor of his or her pain. The patient should be the prime assessor of his or her pain. **(D)***

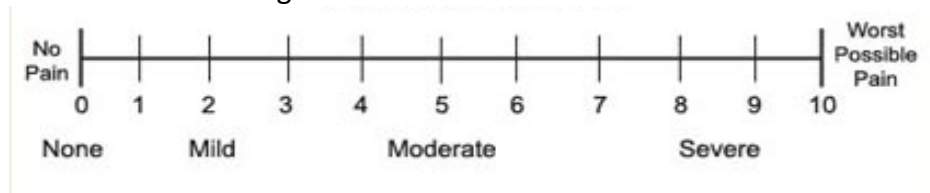
Due to frailty, cognitive impairment or communication deficits not all patients are able to relate the story of their pain. Completion of pain scoring tools may not be possible. In these cases families or health professionals may act as a surrogate.

3.2 How should pain be assessed?

Careful history taking and listening attentively to the patient will usually diagnose the type of pain and this in turn dictates the therapy. The severity of the pain will determine the step of the World Health Organization (WHO) ladder at which the therapeutic intervention will begin.

3.2.1 Detailed history of pain

- a. Location of pain
- b. Number of pains
- c. Intensity of pain : based on patient's self report using;
 - i. 0-10 numerical rating scale or



ii. pictorial scale (Faces Pain rating scale)



- e. Timing of pain: onset, duration, course, intermittent or persistent
- f. Characteristics of the pain (Pathophysiology):
- Nociceptive pain*: injury to somatic & visceral structures with activation of nociceptors
 - Somatic: sharp, well localized, throbbing, aching, stabbing, pressure-like
 - Visceral: diffuse, aching, cramping
 - Neuropathic pain*: injury to peripheral or central nervous system. Described as burning, sharp, shooting, and tingling.
- g. Aggravating & relieving factors
- h. Interference with daily activities: general activity, sleep, mood, appetite
- i. Etiology of pain: Is the pain caused by;
- Cancer
 - Cancer therapy: Radiation, chemotherapy, surgery or procedure related pain
 - Unrelated cause
- j. Analgesic drug history: Current/past pain medication
- What medications?*
 - What dose, how often & how long?
 - What was the response?*
 - Pain relief
 - Side effects
 - Reason for discontinuation
- k. Presence of clinically significant psychological disorder , anxiety or depression
- l. Oncologic treatment: includes
- Chemotherapy : ongoing & prior*
 - Radiation therapy*
 - Surgery*
- m. Medical history
- Presence of other illnesses/ co-morbidities*
 - Pre-existing chronic pain*
- n. Physical examination: Includes general condition, gait of patient, local findings like swelling and inflammation, altered sensation like allodynia, hyperalgesia.

- o. Laboratory & imaging studies to evaluate disease progression:
 - i. All available investigations should be reviewed.
 - ii. In advance cases repeating investigations for new onset pain is not warranted
 - iii. However in select cases if the pain presentation is out of proportion of the clinical scenario, relevant imaging should be asked for.

- p. Reassessment at subsequent follow ups

3.2.2 Pain assessment tools

Patients with cancer pain should have treatment outcomes monitored regularly using numerical rating scales. **(D)***

Observational pain rating scales should be used in patients who are unable to use a self assessment scale. **(C)***

The endpoint of assessment is;

- i. To establish a “Pain Diagnosis”: which includes the etiology and pathophysiology of pain
- ii. To Individualize treatment

Use valid pain assessment tools to evaluate, at regular intervals, both pain intensity and the effectiveness of the pain management plan; document these reassessments. **(A)***

3.2.3 Frequency of assessments

Continual reassessment of the patient is required to identify the effectiveness of pain management, to identify and treat adverse side effects. All patients should be reassessed after 5-7 days of first visit, when possible.

Principles of the World Health Organization (WHO) CANCER PAIN RELIEF PROGRAM

- The patient is started on the appropriate level of the 3 steps WHO ladder for the degree of pain, analgesics are prescribed.
 - Step 1: Paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs)
 - Step 2: Weak Opioids e.g. codeine, tramadol
 - Step 3: Strong Opioids e.g. Morphine
- Oral route of drug delivery is advocated.
- A patient’s treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain. Prescription of analgesics should always be adjusted as the pain severity alters. If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency.
- All patients with moderate to severe cancer pain, regardless of aetiology, should receive a trial of opioid analgesia.
- Chronic pain in patients with cancer is usually continuous and where this is so, therapeutic plasma levels of analgesics should be maintained by giving the drug at regular intervals according to its pharmacokinetic and pharmacodynamic profile not as PRN basis.
- Appropriate analgesia for breakthrough pain must be prescribed.

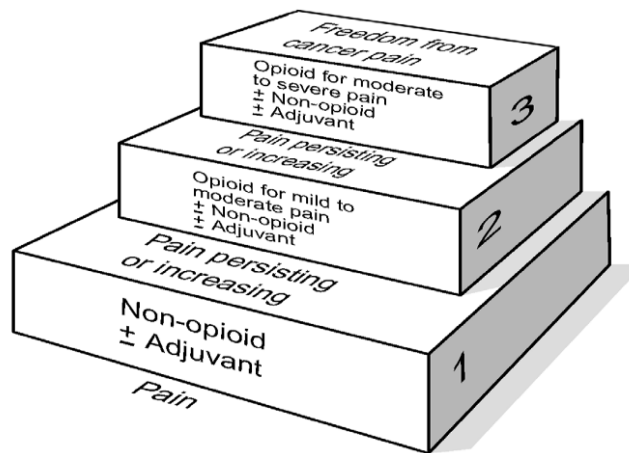


Figure 1: World Health Organization analgesic ladder

II. Guidelines for prescribing Non-opioid analgesics

- Paracetamol , NSAIDs may be used at any stage of WHO ladder
- Used synergistically and produce better pain relief. Paracetamol and / or NSAID should be used unless contraindicated (A)

a) Paracetamol:

Paracetamol works as a weak prostaglandin inhibitor. It achieves this by blocking the production of prostaglandins, thereby blocks pain message to the brain and at source of pain, hence has different action from Aspirin and NSAIDs (non-steroidal anti-inflammatory drugs). Paracetamol can be used by patients for whom NSAIDs are contraindicated, including those with asthma or peptic ulcers. Because there are few interactions with other medications, paracetamol can be taken by people with sensitivity to aspirin. Standard safe dose is 1000mg four times a day or upto 4 gm/day in a normal healthy adult.

b) NSAIDs:

Use any NSAID that the patient has found effective and tolerated well in the past, otherwise consider ibuprofen to the maximal dose.

Ibuprofen, 400 mg four times a day (daily maximum = 3,200 mg)

Note that the potential adverse effects of chemotherapy, such as hematologic, renal, hepatic, and cardiovascular toxicities, can be increased by the concomitant prescription of NSAIDs.

Opioid analgesics are a safe and effective alternative analgesic to NSAIDs.

i. Monitoring for NSAID toxicities:

- Baseline blood pressure, BUN, creatinine, liver function studies [alkaline phosphatase, LDH, SGOT, SGPT], CBC, and fecal occult blood
- Repeat every 3 mths to ensure lack of toxicity

- ii. NSAID and toxicities:
Age > 60 y, compromised fluid status, multiple myeloma, diabetes, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporine, cisplatin) and renally excreted chemotherapy
- iii. Treatment of toxicity :
 - If patient develops gastrointestinal upset, peptic ulcer , hemorrhage or vomiting, consider discontinuing NSAID or changing to selective COX-2 inhibitor. COX-2 inhibitors are associated with lower incidence of GI adverse effects and do not inhibit platelet aggregation, however, they have not been demonstrated to have reduced renal adverse effects. Consider adding antacids, H2 receptor antagonists, omeprazole.
 - Discontinue NSAID if liver function studies increase 1.5 times the upper limit of normal.
 - If congestive heart failure or hypertension develops or worsens, history of cardiovascular disease, discontinue NSAID.
 - Risk of bleeding may significantly increase in patients on anticoagulants, such as warfarin or heparin, if NSAIDs are given.

III. Guidelines for prescribing opioids in Cancer Pain:

1. Intent:
 - a. To lay down guidelines for
 - b. the use of opioid analgesics in patients with cancer pain
 - c. the use of rescue doses for breakthrough pain
 - d. Conversion / rotation from one opioid to another opioid
 - e. Conversion of oral to transdermal route
 - f. the management of opioid induced side effects
2. Scope of these guidelines
 - a. To standardize prescription of opioids across the service & hospital
 - b. To prevent and actively manage opioid related side effects
3. General principles of opioid prescription (APPENDIX I)
 - a. The WHO analgesic ladder should be followed while treating pain in patients with cancer
 - b. Start treatment at the WHO analgesic ladder step appropriate to the severity of pain
 - c. Oral route preferred. Other routes (S.C, I.V, Transdermal, buccal, transmucosal, PR) can be used when indicated, if oral route cannot be used
 - d. Intramuscular route not recommended as it is painful and unreliable
 - e. Analgesia should be prescribed on a "regular" and not on an "as required" basis
 - f. Appropriate analgesia should be prescribed for breakthrough pain

- g. Mixed agonists-antagonists have limited usefulness in cancer pain and should not be prescribed in combination with opioid agonists. Could precipitate withdrawal in opioid dependent patients
 - h. Reassure patients about the low probability of addiction to opioids & encourage to adhere to treatment regime
4. Principles of opioid maintenance therapy
- a. Extended release or long-acting preparations on a regular schedule to provide background analgesia once dose requirements are stable
 - b. Rescue doses ($1/6^{\text{th}}$ of the 24 hr dose of morphine) in the form of an immediate acting/ short acting opioid preparation should be prescribed for breakthrough pain or acute exacerbations related to activity
 - c. The same opioid, if possible, should be used for breakthrough and “around-the-clock” dosing
 - d. Increase the dose of the “around-the-clock” preparation if patient requires more than 3 breakthrough analgesic doses
 - e. Dose increase, if necessary
 - i. Immediate release preparation: after every 24 hours
 - ii. Controlled release or extended release preparations: after 48 hours
 - f. Each dose increment can be set at 33-50% of the pre-existing dose and should be accompanied by a proportionate increase in the rescue dose.
 - g. Transmucosal fentanyl should be used only in opioid tolerant patients and initiated with the lowest dose
 - h. For patients who experience inadequate pain relief or unacceptable side effects : Consider Opioid rotation
5. Conversion from one opioid to another (Opioid rotation)
- a. For patients with inadequate pain relief and/or intolerable side effects while on strong opioids: Consider switching to a different opioid
 - b. Determine the amount of current opioid taken in last 24 hours that produced good pain relief
 - c. Calculate the equianalgesic dose of the new opioid
 - d. An equianalgesic table (APPENDIX II-IV) should be used when switching to ensure equivalency
 - e. Safe to reduce the dose of the new opioid by 25% to 50% when switching, if pain relief was good
 - f. If previously pain relief was inadequate, may begin with 100% of equianalgesic dose or increase by 25%
 - g. Assess regularly for efficacy & side effects.
6. Principles for prescription of Transdermal fentanyl
- a. Pain should be well controlled on a short acting opioid prior to starting a Transdermal fentanyl patch.
 - b. Should be used only in opioid tolerant patients

- c. Not recommended for unstable or poorly controlled pain
 - d. Fever and use of warming devices (warming blankets etc) accelerate absorption from the patch, hence are contraindications for its use.
 - e. Analgesic duration is usually 72 hours, but some patients require replacement every 48 hours
7. Conversion from morphine / codeine to transdermal fentanyl
- a. Select mcg/hr dose of transdermal fentanyl based on the last 24 hr dose of Morphine or codeine (APPENDIX III)
 - b. An “as- required” dose of immediate release/ short acting morphine should be prescribed and will be needed particularly during the first 8 to 24 hours
 - c. The patch dose can be increased after 3 days based on the amount of daily ‘as-required” opioid needed.
8. Management of side effects
- a. Constipation
 - i. Should prescribe a stimulant laxative ± stool softener (Liquid paraffin + Na picosulphate)
 - ii. Increase dose when increasing dose of opioids
 - iii. Adequate fluid and dietary fiber intake
 - iv. Add another laxative, e.g.; lactulose 30-60 ml/day, if constipation persists
 - v. Severe constipation: Sena compounds (Senasoft) initiate with 1hs.
 - vi. Enema, if fecolith
 - b. Nausea
 - i. Prophylactic use of anti-emetics may be recommended in emesis prone patients
 - ii. If nausea develops;
 - 1. Rule out other causes (constipation, CNS pathology, Chemotherapy, radiation therapy, hypercalcemia)
 - 2. Consider metoclopramide 10 mg PO every 6-8 hrs, or in refractory cases, haloperidol 0.5-1 mg PO every 6-8 h may be added
 - 3. If nausea present despite above, add an “around-the-clock” serotonin antagonist e.g.; ondansetron 8 mg PO TDS.
 - c. Pruritis
 - i. Assess for other causes (other medications)
 - ii. Antihistamines to be used. Diphenhydramine (Benadryl) 25-50 mg IV or PO every 6 hrs or promethazine (phenargan)12.5 -25mg PO every 6 hrs
 - iii. If persisting despite above, consider continuous infusion of naloxone 0.25 mcg/kg/h and titrate up to 1 mcg/ kg/ hr without decreasing analgesic efficacy

- d. Sedation
 - i. Assess for other causes (CNS pathology, other medications, hypercalcemia, dehydration, sepsis, hypoxia)
 - ii. Reduce dose of opioid
 - iii. Consider rotation
 - iv. Increase non-opioid analgesics where feasible
 - v. CNS stimulants e.g.; Caffeine 100-200 mg PO every 6 hrs could be considered

- e. Respiratory depression
 - i. Shallow breathing & unresponsiveness. Consider naloxone infusion. Dilute 1 ampoule (0.4 mg/ml) in 9 ml of normal saline to a total volume of 10 ml. Give 1-2 ml (0.04-0.08 mg) every 30-60 seconds until symptoms improve.
 - ii. If no improvement, consider other causes for change in CNS status

- f. Delirium
 - i. Assess for other causes (e.g.; hypercalcemia, CNS metastases, other psychoactive medications)
 - ii. Reduce dose of opioid if feasible
 - iii. Haloperidol 0.5-2 mg PO or IV every 4-6 hrs

- g. Cognitive impairment
 - i. Stable doses of opioids (> 2 weeks) unlikely to interfere with psychomotor & cognitive function.
 - ii. Monitor during initial titration

- h. Usually tolerance develops for all side-effects with time, except constipation. If persists, consider opioid rotation or maximize non-opioid / neuraxial analgesics/ neuroablative procedures.

9. Co-morbidities

- a. Liver disease
 - i. All opioids are metabolized in the liver
 - ii. Opioid clearance reduced, bioavailability and half-life increased
 - iii. Risk of adverse effects because of higher-than-expected plasma concentrations
 - iv. Metabolism of morphine not significantly altered
 - v. Avoid use of Acetaminophen in these patients

- b. Renal disease
 - i. Active metabolites of propoxyphene (norpropoxyphene), morphine (morphine-6-glucuronide [M6G], morphine-3-glucuronide [M3G] and nor morphine) and codeine may accumulate

- ii. High levels of M3G may cause hyperalgesia and myoclonus
- iii. Use opioids with caution
 - 1. Reduced dose and / or
 - 2. Reduce frequency of administration
- iv. Avoid using morphine and codeine in patients with renal failure
- v. Fentanyl, Alfentanil and Buprenorphine are the safest opioids in patients with chronic renal disease stage 4 or 5 (GFR <30 ml/min). Transdermal fentanyl is the opioid of choice

c. Dysphagia, Intestinal obstruction: Transdermal Fentanyl patches are the treatment of choice. Start with the lowest strength patch (12.5 mcg) in opioid naïve patients. If already have taken morphine or other oral opioid, then start appropriate dose of Transdermal fentanyl referring to the conversion chart (APPENDIX III)

APPENDIX I: Basic pharmacology of opioids (available in India)

Drug	Onset of pain relief	Time to peak pain relief	Duration of pain relief	Bioavailability (range)	Peak plasma level	Half life
Codeine	30-60 min	45-60 min	4-6 hr	40%(12-84%)	1-2 hr	2.5-3.5 hr
Tramadol	30 min	180 min	4-6 hr	75%	2 hr	6 hr
Morphine	20-30 min	60-90 min	3-6 hr	35% (15-64%)	15-60 min	1.5-4.5 hr

APPENDIX II: Oral to parenteral opioid equivalences table

OPIOID	Dose (mg) equianalgesic to 10 mg Morphine		IV to PO FACTOR	Duration Of Action
	PARENTERAL DOSE	ORAL DOSE		
Codeine	130 mg	200 mg	1.5	3-4 hr
Morphine	10 mg	30 mg	3	3-4 hr
Tramadol	---	50-100 mg	---	3-7 hr

APPENDIX III: Dose conversion table from other opioids to Transdermal fentanyl

Transdermal Fentanyl	Morphine		Codeine	
	IV/Sub cut	Oral	IV/Sub cut	Oral
25 mcg/h	20 mg/day	60 mg/day	130 mg/day	200 mg/day
50 mcg/h	40 mg/ day	120 mg/day	260 mg/day	400 mg/day

75 mcg/h	60 mg/day	180 mg/day	390 mg/ day	600 mg/ day
100 mcg/h	80 mg/ day	240 mg/day	520 mg/day	800 mg/day

APPENDIX IV: Dose conversion ratios (While switching opioids)

Current opioid (oral)	New opioid (oral)	How to calculate 24 hour dose
Codeine	Morphine	Divide by 10
Tramadol	Morphine	Divide by 5

Reference:

Control of pain in adults with cancer: Summary of SIGN guidelines. BMJ 2008, 337:1106-1110)

IV. Guidelines for prescribing adjuvants:

What is an adjuvant? An adjuvant is a medication that is not primarily designed to control pain, but can be used for this purpose. They are a diverse group of drugs that includes antidepressants, anticonvulsants (antiseizure drugs), and others.

a) Antidepressants

The best studied adjuvant analgesics are the tricyclic antidepressants (TCAs), such as amitriptyline , and desipramine. These drugs have been shown to relieve pain independent of their effects on depression; that is, patients who are not depressed may experience pain relief. Once the correct dose is found for the individual patient, favorable results are usually seen within a week; however, side effects, including weight gain, dry mouth, blurred vision and constipation, are possible. They are prescribed either alone or with anticonvulsant in patients with neuropathic pain

b) Anticonvulsants

Drugs that are primarily used to treat epilepsy (seizures) have been used to treat nerve pain conditions. Many anticonvulsant drugs have been shown in clinical studies to be effective. The most common side effects associated with these drugs are mental clouding and sleepiness. Gabapentin or pregabalin are two agents which are used commonly.

c) Alpha-2-Adrenergic Agonists

Currently, there are two alpha-2-adrenergic agonists that have some evidence as pain relievers: tizanidine and clonidine

d) Local Anesthetics

Intravenous infusion of a local anesthetic is a special technique that may be used by pain specialists. Mexilitine has shown to be effective in chronic nerve pain syndromes with

lancinating type of pain. Other oral local anesthetics are also used. Lignocaine transdermal patch 5% is used in post herpetic analgesia

e) Steroids

Corticosteroids can be used as an effective analgesic for treating some cancer pain syndromes. Used in pain due to raised intracranial tension, nerve compression, epidural spinal cord compression, pain due intestinal obstruction, plexopathies and complex regional pain syndrome (reflex sympathetic dystrophy).

f) Other Adjuvants

- Baclofen as a muscle relaxant, is also used to treat nerve pain syndromes.
- Drugs that block wide dynamic range neurons involved in the experience of pain, the N-methyl-D-aspartate (NMDA) receptor, may also be used as very useful analgesic in refractory neuropathic pain conditions. Examples: Ketamine (anesthetic), dextromethorphan (the cough suppressant, but at higher doses than those needed to block cough)
- Bisphosphonates: is considered for use as part of the regime to treat pain in patients with metastatic bone pain **(B)**

V. Guidelines for the management of Neuropathic Pain

1. Aim:

- a. To lay down guidelines for the;
- b. Assessment of neuropathic pain in patients with cancer
- c. Appropriate treatment regimens based on the underlying mechanisms causing pain.

2. Scope of these guidelines

- a. Help clinicians to assess and manage neuropathic pain in cancer effectively.
- b. To minimize risk of side effects due to analgesics
- c. To standardize prescriptions and procedures
- d. To individualize treatment with the goal of maximizing function & quality of life

3.1 What is neuropathic pain?

- e. Pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system (Neuropathic Pain Working Group 2006)
- f. Common neuropathic syndromes in cancer
- g. Brachial plexus neuropathies
- h. Chemotherapy-induced neuropathy: Cisplatin, Oxaliplatin, Paclitaxel, Thalidomide, Vincristine, Vinblastine
- i. Cranial neuropathies, Post herpetic neuropathy
- j. Post-radiation plexopathy
- k. Surgical neuropathies

- l. Phantom limb
- m. Post-mastectomy syndrome
- n. Post-thoracotomy syndrome

3.2.1 How to diagnose neuropathic pain?

In the pain clinic, assessment of a pain patient with suspected neuropathic pain aims at recognition of neuropathic pain, localizing the lesion, and diagnosing the causative disease or event. Nerve compression has been reported to be the most common cause of neuropathic pain in cancer patients (79%), followed by nerve injury (16%) and sympathetically mediated pain (5%).

- Description/ Characteristics of pain:
 - i. Spontaneous (Stimulus independent):
 1. burning
 2. shooting
 3. stabbing
 4. Electric shock-like pain
 5. Pin & needles
 6. Dysaesthesias (abnormal and unpleasant sensations)
 7. Paraesthesias (abnormal, but not unpleasant sensations)
 - ii. Stimulus evoked pains (Elicited by mechanical, thermal or chemical stimulus):
 1. Hyperalgesia (increased response to normally painful stimulus)
 2. Mechanical allodynia (pain from non-painful stimuli)
 3. Inability to tolerate cloth, air from fan or air conditioning vent touching the skin
 4. Cold allodynia (pain evoked by cold stimulus)

3.2.2 Pain assessment tools:

- **painDETECT questionnaire**: this simple scoring system is available in English, Hindi, Marathi and other many Indian languages, can be completed by individual patients, helped by their relatives. A diagnosis of neuropathic pain can be made. A total of score points are estimated out of 35 points. < 12 : negative , 13-18: possible, > 19 : positive neuropathic pain.

3.3 Frequency of assessments

Review regularly, at least once a week, to determine the effectiveness of treatment. If patient is in hospital, more often twice a week.

4 Management of neuropathic pain

- a) Initiate pharmacotherapy with only one drug at a time

- b) Neuropathic pain can be treated by unconventional analgesics (adjuvants) which are primarily not analgesics e.g. antidepressants, anticonvulsants or combined with conventional medications such as opioids.
- c) Adjuvant analgesics e.g. tricyclic antidepressants (TCAs) and anticonvulsants are used as first line drugs.
- d) If pain relief is inadequate with one drug, TCA+ anticonvulsants (Gabapentin or pregabalin) may be used.
- e) Selective serotonin reuptake inhibitors (SSRI) or selective nor epinephrine reuptake inhibitors (SNRI) may be added as 2nd line drugs e.g. duloxetine, lamotrigine.
- f) Aggressive side effects management is required to open the therapeutic window.
- g) Opioids may be added as third line drug if the combination fails to provide satisfactory relief.
- h) Capsaicin cream, lidocaine 5% patch or Inj ketamine may also be used to obtain optimum pain relief. The starting dose and any titration of each pharmacological intervention should be properly planned in individual patient, taking into consideration the potential side-effects and interactions with other medication.
- i) Non-Opioids: NSAIDs and Paracetamol have a limited use in neuropathic pain.
- j) However patient may have associated nociceptive pain which may respond to the same.
- k) Interventional treatments for neuropathic pain should be offered to any patient whose pain is not adequately treated with first and second line drugs or for patients with intolerable side-effects from medication
- l) Invasive treatments should usually be carried out as part of a multidisciplinary treatment plan

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VI. Guidelines for management of bone metastasis pain:

1. INTRODUCTION

- a) Cancer-induced bone pain (CIBP) is one of the most common types of cancer pain, present in 28-45% of patients with bone metastasis. CIBP often results in hospice or hospital admission and is associated with reduced quality of life, increased psychological distress and decreased physical and social functioning.
- b) The degree and location of bone metastases do not necessarily correlate with the severity of pain. Some patients have widespread bone metastases but minimal pain, whereas others have minimal bone metastases but severe pain. Apart from CIBP, the other complications of cancer-induced bone disease are hypercalcaemia, cytopaenias and risk of pathological fractures.
- c) CIBP does not exist as a single entity, but is instead a combination of background pain and breakthrough pain.
- d) Almost half of breakthrough pain episodes were rapid in onset (<5 min) and short in duration (<15 min). Forty-four per cent of patients with breakthrough pain had pain that was unpredictable
- e) Up to 45% of patients with CIBP report poor pain control

2. DIAGNOSIS:

A cancer patient requires a comprehensive evaluation to determine the etiology and site of the specific pain syndrome involved bone metastasis.

- i. Plain X-ray: Lytic, nodular or rounded, well-circumscribed sclerotic lesions are seen on a plain x-ray.
- ii. CT-scan: Is extremely useful to confirm isolated lesions, assess the extent of soft tissue involvement and to differentiate between metastasis and degenerative changes.
- iii. Bone scan: Is a sensitive imaging tool to detect bone metastases early and still the optimum method for diagnosis. However, small deposits (less than 2 mm) may be missed.
- iv. MRI: Useful to image the spine, vertebral bodies, paraspinal area including the soft tissue component and spinal cord compression. It can differentiate between benign and malignant vertebral collapse⁴.
- v. PET-Scan: Positron emission tomography uses radioactive F-fluorodeoxyglucose (FDG) as a tracer to highlight metabolically active cells. It is not specific for bone metastases and will also identify any area with increased metabolic rate and glucose turnover. The test is now used as an investigational tool for most cancers⁵.

- vi. Biochemical markers: The biochemical markers currently available lack specificity and are of no value in the diagnosis of skeletal metastasis. They include: alkaline phosphatase, urinary hydroxyproline and urinary hydroxyproline: creatinine ratio.

3. TREATMENT

- a. The current treatment options for CIBP are wide-ranging and include external beam radiotherapy, opioid analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates. In addition, local surgery and anaesthetic techniques are used. However, each of these treatment options is accompanied by limitations in their use.
- b. Radiotherapy is the gold standard treatment of CIBP. Complete pain relief is only achieved in about 25% of patients, whereas 50% of patients will achieve 50% pain relief.
- c. NSAIDs, being anti-inflammatory drugs are important in the treatment of CIBP based on experience rather than strong evidence.
- d. Opioids are an effective therapy for background pain in CIBP. However, a normal release morphine will probably be ineffective in patients with rapid-onset, short duration breakthrough pain due to its slow onset of action.
- e. Alternative routes of fast acting opioids are transnasal(butorphenol),transmucosal (fentanyl).
- f. Bisphosphonates are used to reduce skeletal morbidity from bone metastases and for analgesia in CIBP.
- g. Pain produced by bone metastases influences the nervous system peripherally and centrally. Spontaneous breakthrough pain which may occur at rest in bone metastasis, may poorly respond to opioids.

References:

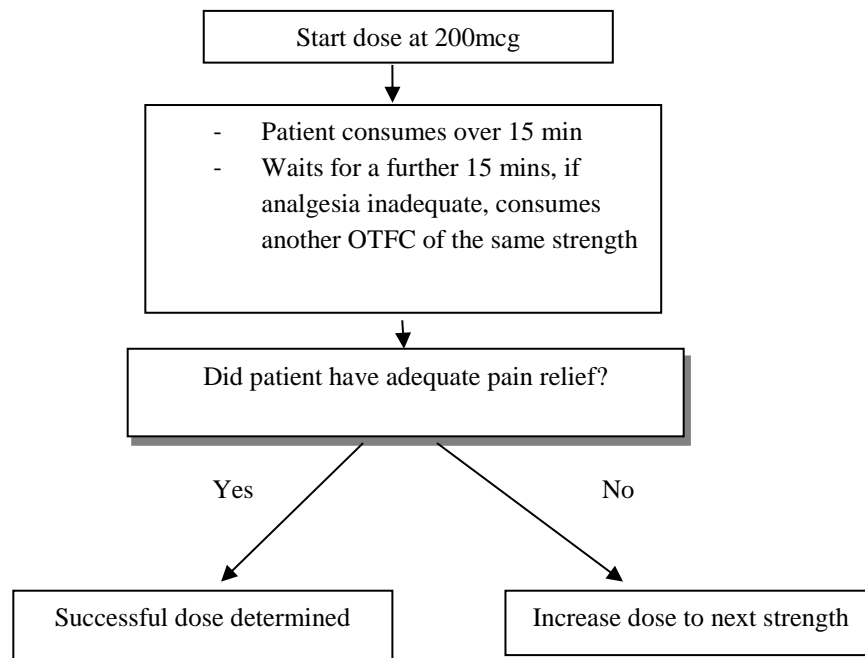
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VII. Guidelines for the management of Breakthrough Pain (BTP) in cancer

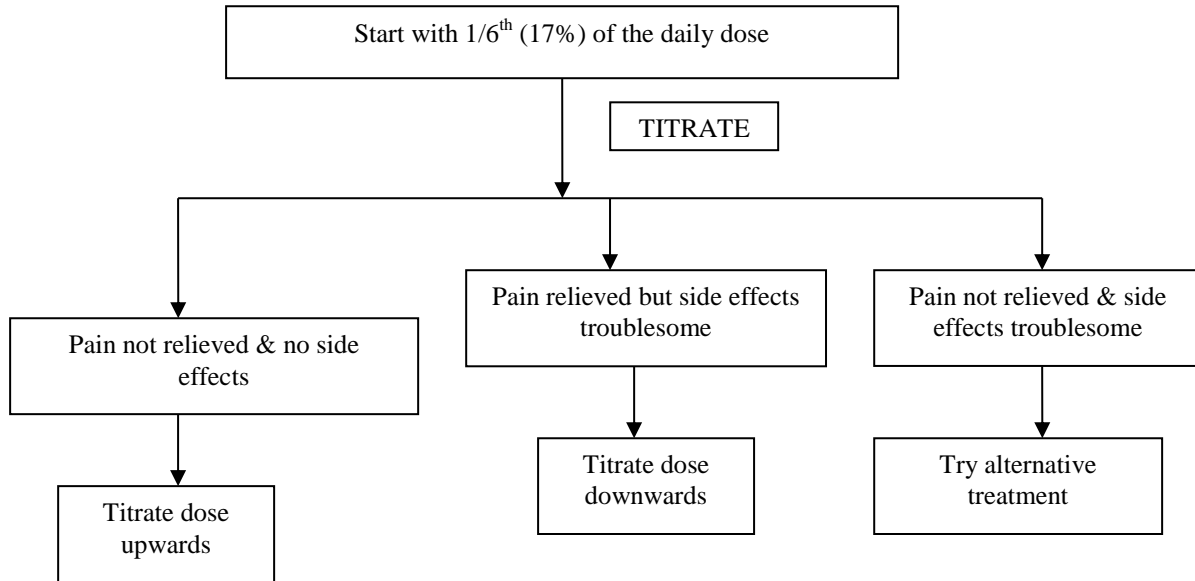
1. Aim:
 - To lay down guidelines for
 - a. Identification & assessment of breakthrough pain in cancer patients.
 - b. Appropriate treatment regimens for the management of such pain
 - c. To reduce the intensity, severity & impact of each bout of pain
2. Definition: A transitory exacerbation of pain experienced by the patient who has a relatively stable and adequately controlled baseline pain (Portenoy et al 2004). Prevalence of BTP is 20- 65%.
3. What are the types of BTP?
 - a. Incident pain: precipitated by movement/coughing
 - b. Spontaneous pain : occurs in absence of a specific trigger & at random
 - Should be differentiated from end-of-dose pain which occurs,
 - just prior to the scheduled dose of analgesia,
 - Either due to an inadequate analgesic dose or too long an interval.
 - Gradual onset.
4. How to identify breakthrough pain?
 - a. Rapid onset
 - b. Severe intensity
 - c. Variable duration (usually 30 minutes)
5. Assess
 - All patients with cancer pain for presence of BTP (D)
 - Each episode of breakthrough pain for;
 - a. Frequency
 - b. Duration
 - c. Pain intensity
 - d. Precipitating factors
 - e. Baseline pain treatments and their effectiveness
 - f. Re-assess to determine;
 - i. Efficacy & tolerability of treatment.
 - ii. Change in nature of the pain
6. Management of BTP
 - a. Optimize the round-the-clock analgesia by titrating opioids
 - b. Should always prescribe rescue analgesia and teach the patient how to use it.
 - c. Opioids are the rescue medications of choice. Little evidence to support the use of non-opioid analgesics for breakthrough pain.

- d. The opioid should be chosen based on its pharmacokinetic properties. If possible, rescue dose should be of the same opioid used for baseline pain (Mercadante et al 2002)² but there are no compelling reasons for using the same opioid.
- e. European Association of Palliative Care (EAPC) recommendations are to start with 1/6th (17%) of the daily dose, and subsequent titration according to clinical effect.(Hanks et al 2001)³.
- f. The dose of opioid rescue medication should be determined by individual titration(Zeppetella, 2006)⁴ **(B)**
- g. Incident pain: pre-emptive use of a short acting opioid, 30 minutes before the activity which precipitates pain. (Mc Carberg, 2007)⁵.
- h. Spontaneous pain: Oral transmucosal fentanyl citrate (OTFC) found to be an effective treatment for breakthrough pain by a recent Cochrane review. (Zeppetella, 2006)⁴
- i. End-of-dose failure: alter the around-the-clock medication to increase the dose or shorten the dosing interval (McCarberg, 2007)⁵.
- j. Transdermal fentanyl: duration of action- 72 hours. In some patients (3-43%), duration is between 48-72 hrs & may require breakthrough medications after 48 hrs. Replace the patch in these patients every 48 hrs rather than 72 hrs instead of increasing the dose of the patch.
- k. More than 4 episodes of breakthrough pain in a day: review the baseline pain management. (Coluzzi, 1998)⁶

APPENDIX V. Management of BTP
OTFC titration (adapted from Zeppetella2005)



APPENDIXVI: Titration to obtain “correct dose” of oral morphine for breakthrough pain



APPENDIXVII: Breakthrough dose of oral morphine for background dose of transdermal fentanyl

Background dose of transdermal fentanyl ($\mu\text{g/hr}$)	Breakthrough dose of oral morphine (mg)
25	< 20
50	25-35
75	40-50
100	55-65
125	70-80
150	85-95
175	100-110
200	115-125
225	130-140
250	145-155
275	160-170
300	175-185

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VIII. Guidelines for interventional Pain management:

Indications:

- a) Usually nerve blocks are indicated when even oral strong analgesics do not provide even 50% pain relief and there are intolerable side effects.
- b) If interventional approaches are appropriate; evaluate which dermatomal site of pain can be relieved. Verify interventional technique which will provide sufficient benefit for the diagnosed pain syndrome.
- c) Pain likely to be relieved with nerve block (eg, pancreas/ upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve, or peripheral nerve)

Commonly used interventional procedures

- 1) Neurodestructive procedures for well-localized pain syndromes
 - a) Head and neck: peripheral nerve block
 - b) Upper extremity: brachial plexus neurolysis
 - c) Thoracic wall: epidural neurolysis, intercostal neurolysis
 - d) Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy
 - e) Midline pelvic pain: superior hypogastric plexus block
 - f) Rectal pain: intrathecal neurolysis, midline myelotomy or superior hypogastric plexus block, Ganglion Impar
 - g) Unilateral pain syndromes: cordotomy
 - h) Consider intrathecal L/S phenol block
- 2) Radiological interventions: Percutaneous vertebroplasty/kyphoplasty, Radiofrequency ablation for bone lesions
- 3) Neurostimulation procedures for cancer-related symptoms (ie, peripheral neuropathy)
- 4) Regional infusions (requires spinal intrathecal infusion pump) easy to internalize implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide

Contraindications ;

Infection, coagulopathy, very short or lengthy life expectancy, distorted anatomy, patient unwillingness, medications that increase risk for bleeding,(eg, use of anti-angiogenesis agents such as bevacizumab) or technical expertise for performing interventions is not available.

IX. Guidelines for pain management at end of life:

1.Introduction

- a) Many patients at the end of life are unable to verbally report pain using standardized scales. In this situation, evaluate behavioral cues such as facial grimacing, guarding, or vocalizing.
- b) Rule out other potential causes of distress such as constipation, urinary distension, or emotional and spiritual distress
- c) Administration of opioids may be complicated by the inability to swallow. Alternate routes of administration include buccal, sublingual, rectal, subcutaneous, or intravenous delivery.
- d) Doses may be decreased in some cases, as organ system failure leads to reduced excretion of the drug and or its metabolites, as well as other factors.
- e) Myoclonus may occur when higher doses of opioids are administered, particularly in the face of renal dysfunction. Reducing the opioid dose or rotating to another opioid can be effective, and adding benzodiazepines can be helpful.

2.Management:

- a) ☑Education of family members regarding signs of impending death will assist in reducing their anxiety.
- b) ☑Collaborate with other members of the health care team (e.g., social workers, chaplains, and nurses)
- c) Provide emotional support to the dying patient and his or her family members.
- d) ☑Provide reassurance and role model comforting activities.
- e) ☑Honor the patient's culture; respect cultural preferences and rituals.
- f) ☑Consider the developmental stage of any children involved (patients, siblings, children, or grandchildren) when communicating about death.
- g) ☑Identify those family members at risk for abnormal grief reactions and refer them for counseling and support.

References:

Sykes N, Thorns A. The use of opioids and sedatives at the end of life. *Lancet Oncol* 2003;4:312–8.

X. Guidelines for pain management in cancer survivors:**1. INTRODUCTION:**

A large number of disease-free cancer survivors live with pain or neuropathies induced by treatment or by the cancer itself.

Sometimes these conditions resolve over time, but irreversible damage to tissue and nerves can cause pain and neuropathy to progress and persist indefinitely.

Because health care professionals may not recognize these as delayed problems or know how to identify those at greatest risk, many of these conditions go undiagnosed and untreated.

Most chronic pain syndromes and neuropathies experienced by disease-free survivors of cancer originate from

- an injury to peripheral nerves from surgical trauma,
- neurotoxicity of chemotherapeutic agents
- radiation-induced damage to nerves

Other sources of persistent or intermittent pain include:

- i. myofascial pain dysfunction syndrome, which is characterized by trigger points in muscle or at the junction of muscle and fascia that refer pain to other areas of the body, and which is associated with breast, thorax, and head and neck surgery in cancer survivors.
- ii. fistula formation following pelvic surgery.
- iii. chronic inflammation, such as radiation-induced enteritis or proctitis.
- iv. osteoradionecrosis, a radiation-induced demineralization and vascularization of the bone.
- v. Persistent nerve damage from tumor infiltration of nerves.

2. TREATMENT:

Anticonvulsants, tricyclic antidepressants, and opioids can be effective for alleviating neuropathic pain. Novel pharmacologic agents such as neuroprotective compounds e.g. amifostine, glutamine, and glutathione, and neurotrophic factors (such as nerve growth factor) can also be effective. Vitamin E has shown some promise in prophylaxis of

chemotherapy- induced peripheral neuropathy with cisplatin and paclitaxel. Less is known about nonpharmacologic and alternative therapies.

References:

[Levy MH](#), [Chwistek M](#), [Mehta RS](#). Management of chronic pain in cancer survivors, [Cancer J](#). 2008 Nov-Dec;14(6):401-9.

MALIGNANCIES OF GASTROESOPHAGEAL JUNCTION (Adenocarcinoma GEJunction)

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CASE DEFINITION

Tumors having their center 5-cm proximal or distal to the anatomic cardia are classified as malignancies of the GE junction. Histologically they can be adenocarcinoma or squamous Cell carcinomas. ***Squamous cell Carcinomas are treated as carcinoma esophagus, hence all the further discussion will be restricted to Adenocarcinoma GE Junction***

Incidence of adenocarcinoma GEJunction is on the rise and is emerging as a new disease. Carcinoma esophagus is now more common in the lower third and there is marked increase in the carcinomas of proximal stomach creating the new identity of Adenocarcinoma of GEJunction. There is a rise in the incidence of almost 10% per year, more the non endemic areas or European world.

Unlike Squamous cell carcinoma, Adenocarcinoma GEJunction is found in the developed countries and in patients of upper socio economic status and has a better prognosis than the SCC esophagus. It is associated with Obesity, High Body mass index, GERD and Barrets Esophagus.

Barrets Esophagus –this defined as the presence of intestinal metaplasia (mucin producing goblet cells) in columnar cell lined epithelium that replaces the squamous epithelium of the distal esophagus. This specialized metaplasia confirmed on histopathology is mandatory for diagnosis of barrets Esophagus which confers a 40-125 fold higher risk for developing adenocarcinoma GEJunction and is the single most important risk factor.

Classification of Barrets Esophagus

Siewart's Classification

Type I – Epicenter of tumour or more than 66% of the tumor mass located >1 cm above the anatomic GE junction

Type II- Tumor epicenter located within 1-cm proximal and 2-cm distal to the GE junction

Type III- Tumor epicenter or more than 66% of the tumor mass is located more than 2 cm below the anatomic GE junction

Revised Seiwart's classification of 2000

Type I adenocarcinoma, which may infiltrate the GE junction from above

Type II adenocarcinoma, which arises from the GE junction

Type III adenocarcinoma, or subcardial gastric carcinoma, which infiltrates up to the GE junction from below

WHEN TO SUSPECT

Presenting Symptoms

Most common presenting feature of adenocarcinoma GE Junction is dysphagia, initially to solids and then to liquids. Other symptoms that patient may present with are

- Odynophagia
- Dyspepsia
- Loss of weight
- Anorexia
- Left supraclavicular node
- Haematemesis
- Vomiting

Differential Diagnosis

All elderly patients presenting with long standing dyspepsia and features of GERD or with anorexia, loss of weight and dysphagia, should be investigated for carcinoma esophagus

Common differential diagnosis are

- GERD
- Barrets Esophagus
- Carcinoma Stomach
- Carcinoma Esophagus
- Achlasia cardia
- Hiatus Hernia
- Esophageal diverticulum or stricture

Examination

Besides the routine general and systemic examination, patient should be assessed for

- General condition
- Nutritional status
- Pallor
- Left supraclavicular node

WORKUP FOR DIAGNOSIS AND STAGING

Investigations-

Following investigations are mandatory for assessing any suspected or diagnosed case of Carcinoma Esophagus

- Upper GI Endoscopy –To see for
 - Presence of growth
 - Site of growth
 - Nature of growth
 - Vertical and circumferential extent of growth
 - Passage of scope beyond the growth

- Status of stomach
- Presence of Barrets esophagus
(Naso gastric feeding tube to be placed if esophageal lumen found to be obstructed)
- Endoscopic Biopsy- from representative site. Following to be assessed
 - Histology
 - Differentiation
 - Presence of Barrets esophagus
- CECT Chest and upper abdomen-To see for
 - Vertical and Horizontal extent of diseases
 - Adherence or infiltration of surrounding structures like trachea, main bronchus, aorta and pericardium
 - Para esophageal nodes
 - Involvement of GE Junction and proximal stomach in the lower third esophageal and GEJunction cancers
 - Liver metastasis
 - Pericardial and plural effusion
 - Ascitis
 - Perigastric lymphnodes
- FNAB of left supraclavicular node if present and left scalene pad of fat biopsy if nodularity felt
- Hb, TLC, DLC, blood grouping
- Biochemistry-LFT,RFT, Blood Sugar, Electrolytes and platelets
- ECG
- Ba Swallow-

Optinal Investigations

Following Investigations are optional and may be done in tertiary care centres where facilities are available

- Endoscopic Ultrasound
- Endoscopic ultrasonographic FNAB of paraesophageal nodes
- PET Scan
- Her 2 Ney receptor study by FISH technique on biopsy specimen

STAGING (AJCC 7th Ed 2010)

- **Tis High grade dysplasia (ca in situ)**

- **T1a** Tumour invades lamina propria or muscularis mucosa
- **T1b** Tumour invades submucosa
- **T2** Tumour invades muscularis propria
- **T3** Tumour invades adventitia
- **T4a** Resectable tumour invading pleura, pericardium or diaphragm
- **T4b** Unresectable tumour invading other adjacent structures,
- **Nx** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1-2 regional lymph nodes
- **N2** Metastasis in 3-6 lymph nodes
- **N3** Metastasis in seven or more regional lymph nodes
- **M0** No Metastasis
- **M1** Distant Metastasis

Group staging

Stage	T	N	M
• 0	T1	N0	M0
• 1A	T1	N0	M0(G1,2)
• 1B	T1	N0	M0(G3)
•	T2	N0	M0(G1,2)
• IIA	T2	N0	M0(G3)
• IIB	T3	N0	M0
•	T1-2	N1	M0
• IIIA	T1-2	N2	M0
•	T3	N1	M0
•	T4a	N0	M0

- **IIIB** **T3** **N2** **M0**
- **IIIC** **T4a** **N1-2** **M0**
- **T4b** **any** **M0**
- **any** **N3** **M0**
- **IV** **any** **any** **M1**

TREATMENT

Neoadjuvant Therapy-All patients with growths T2N0 and beyond should receive 4 # of Neoadjuvant Chemotherapy with two drug regime of any combination including platinum and taxane based drugs can be used too

Surgery-Surgery remains the gold standard in treatment of carcinoma GEJunction Since Surgery involves thoracic surgery and post operative critical care, treatment of GEJunction malignancies should be undertaken where facilities and expertise for thoracic surgery and critical care are available

Contraindications to Resection-Surgical resection should not be considered in the following circumstances

- T4b lesion
- Left supra-clavicular node
- Distant metastasis
- Multi-station bulky nodal mass
- Poor general condition
- Co-morbid medical conditions making patient unfit for anesthesia

Treatment

Treatment of Barrets esophagus

Low grade and High grade dysplasia and Metaplasia can be observed, however Barrets esophagus needs active treatment and close follows. Barrets Esophagus can be treated with Proton Pump inhibitors, Treatment of H pylori infection, Cox Inhibitors. Surgery for GERD and Hiatus hernia prevent formation and progress of Barrets esophagus and in certain circumstances when the segment is large or persistent and progressing then surgical management with resection may have to be resorted to

Treatment of Adenocarcinoma GE Junction

Preoperative laparoscopy may be undertaken before the definitive surgery to assess operability

Segmental Resection-The involved Segment can be excised with a margin of 5 cms through a left thoraco abdominal incision, running along the left 7th rib, upto the umbilicus (Sweet-Garloch incision) Continuity is maintained with gastro esophagectomy and D2 nodal dissection is done

with the resection of the involved segment. This procedure can only be undertaken if the growth is below the diaphragmatic hiatus. Anastomosis can be done handsewn or stapled.

Partial Esophagectomy (Ivor-Lewis Procedure)

This procedure is performed for cancers of the GE Junction involving the lower third of the esophagus with a right thoracotomy and upper midline laparotomy incision. The lower third of esophagus is excised with a margin of 5 cms and anastomosis done with the gastric tube is done in the mediastinum. Mobilization of stomach, formation of gastric tube and nodal dissection remain the same as for segmental esophagectomy

Total Esophagectomy with two field nodal dissection to avoid a mediastinal anastomosis, Total esophagectomy can be performed for GE Junction cancers involving the lower third oesophagus. This includes the removal of complete esophagus, removal of paraesophageal lymph nodes and D2 dissection of gastric lymph nodes, and using a stomach tube as conduit to restore continuity with anastomosis with cervical esophagus in the left side of the neck. This can be done by following two procedures

- Transthoracic Total Esophagectomy (TTE), which includes a right posterolateral thoracotomy for mobilization of esophagus and paraesophageal nodal dissection, mobilization of stomach with D2 nodal dissection of gastric lymph nodes, total esophagectomy, gastric mobilization and formation of gastric tube through an upper midline laparotomy incision and pulling up the gastric tube and anastomosing with proximal esophagus in the left side of the neck. A minimum of 15 nodes should be dissected for adequate nodal dissection. Mobilisation of the esophagus can also be done by ***VATS (Video Assisted Thoracic Surgery)***
- Transhiatal Total esophagectomy (THE) - Is a two step procedure where the thoracotomy is excluded and the esophagus is mobilized blindly through transhiatal route. Adequate paraesophageal nodal dissection is not possible through this procedure, however it avoids a thoracotomy.

Total Gastrectomy with excision of lower third esophagus-Siewert's Type three carcinomas of GE Junction which extend into proximal stomach are treated with total gastrectomy and excision of lower esophagus through a thoraco abdominal incision. Nodal Dissection remains the same and continuity is restored with esophagojejunostomy.

Early Carcinoma of GE Junction-It is rare to find early cases of cancer GE Junction in India, however small T1 lesions can be treated by any of the following procedures

- Endoscopic mucosal resection
- Endoscopic submucosal resection
- Radiofrequency ablation
- Photodynamic therapy
- Cryotherapy

- Local excision

Histopathological Examination-Operative specimen should be examined for the following

- Histology
- Grade
- Margins
- Depth of invasion
- Involvement of extra esophageal tissue
- Lymphovascular invasion
- Number of nodes dissected
- Number of nodes involved
- Perinodal & Perineural infiltration
- Her-2 Neu by FISH in metastatic disease

Adjuvant therapy-

R0 RESECTION

- NO PREOP THERAPY
 - T1,T2,N0 ,OBSERVE
 - T3 /N+, CCRT
- AFTER NACT
 - T2NO, CHEMOTHERAPY
 - T3 /N+ CCRT

R1/R2 RESECTION CCRT

Management of Unresectable tumors or of patients with poor performance status

Definitive CCRT-Concurrent Radiotherapy with 6000Gy of radiotherapy with either of the following combination of drugs.

- Cisplatin and 5FU
- Paclitaxel/Docetaxel with 5FU

Management of Metastatic disease- Metastatic disease is managed with single or two drug regime using chemotherapy platinum,taxanes and 5-FU or supportive care. TRANSTUZUMAB (Herceptine)can be used for HER2 neu + cases

Paliative Care

Obstruction

- Endoscopic lumen restoration
- Laser excision
- Endoscopic lumen enhancement
 - Expandable stents
 - Wire guided balloon dilatation
- Surgical placement of gastrostomy or jejunostomy tube
- Palliative Chemotherapy

BLEEDING

- Endoscopic intervention
- EBRT

PAIN

- Local blocks
- Painkillers

FOLLOWUP

All patients of GEJunction to be followed regularly after completion of treatment, to look for

- Anastamotic Stricture
- Anastamotic recurrence
- Local recurrence
- Nodal recurrence
- Distant Metastasis (Liver and lung)

Frequency of follow-up-Once in every three months for two years and then six monthly till five years post treatment, followed by annual review, lifelong

Following Investigation sto be done at Review

- Hb,TLC,DLC
- LFT
- X-ray chest
- USG Abdomen

- UGI Scopy ,once in a year
- CECT Chest(Optioanl,without any symptoms)

Prevention

- Avoid alcohol and High calori diet
- Avoid obesity
- Treat GERD
- Tretament of Barrets esophagus

FLOWCHART

Tis ----- Endoscopic Mucosal Resection/Ablation
 T1a-----Endoscopic Mucosal Resection/Ablation OR Surgery
 T1b----- Surgery
 T2,3,4 NO,1,2,3-----Neoadjuvant Chemotherapy----- Surgery
 Choice of Surgery
 GEJunction Tumours-Segmental Resection
 GEJunction cancers with Involvement of lower third esophagus ---Partial or total esophagectomy
 GEJunction cancers with involvement of proximal stomach-Total gastrectomy and segmental resection of GEJunction.
 Post Surgery-----R0 RESECTION

- NO PREOP THERAPY
 - T1,T2,NO ,OBSERVE
 - T3 /N+, CCRT
- AFTER NACT
 - T2NO, CHEMOTHERAPY
 - T3 /N+ CCRT

R1/R2 RESECTION----- CCRT
 Poor Performance status-----Definitive CCRT
 Metastatic Disease/recurrence-----Chemotherapy or Supportive care

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NCCN Guidelines 2011
 CANCER-Principles & practice of oncology-Devita (7th & 8th Edition)

Cancer cervix

Introduction : Cervical cancer is major world health problem for the women. It is the third most common cancer worldwide (1,2) and is the most common cancer among women in India. Every year about 1,32,000 Indian women are diagnosed of cervical cancer and over 80,000 die of the disease (IARC estimates) (3). In recent years, molecular biology has firmly established a causal relationship between persistent infection with high risk human papilloma virus (HPV) genotypes and cervical cancer. Other epidemiological risk factors are early age of onset of coitus, larger number of sexual partners , smoking, high parity, prolonged contraceptive use, sexually transmitted disease and chronic immunosuppression(4) Cervical cancer progresses slowly from preinvasive cervical intraepithelial neoplasia to invasive cancer. It is a preventable cancer and successfully treatable when diagnosed in early stages where reported survival is more than 90%(5)

It is important to render the optimal treatment to these women to achieve the best survival as well as the quality of life. Gynae Oncologist / Gynaecologist trained in Oncology for at least one year in prestigious cancer center should preferably treat these patients jointly with Radiation Oncologist & Medical Oncologist as the management includes complex surgeries and multimodality team approach.

Considerations have been given to the available facility for investigations and the expertise available for treating cervical cancer in developing these guidelines.

When to suspect: Symptoms

Precancerous condition & early stage cervical cancer have no symptoms.
Following symptoms require proper evaluation for cervical cancer

Increased vaginal discharge
Contact Spotting / Bleeding
Inter menstrual Bleeding
Postmenopausal Vaginal Bleeding
Pain Lower Abdomen &
Backache

Incidence of the cervical cancer in our country :

1, 32,000 Cases of cervical cancer are diagnosed every year.

Mortality : 80,000 cases die of cervical cancer every year.(IARC)
(3)

Differential diagnosis :

Cervical Polyp, Endocervical / Endometrial polyp presenting at cervix., cervical Leiomyoma & Condyloma cervix

Prevention & Counseling :

Primary prevention :

HPV Vaccination :

Vaccination against HPV-16 and HPV-18 reduces incident and persistent infections with efficacy of 91.6% (95% CI, 64.5–98.0) and 100% (95% CI, 45–100), respectively.(6)

Barrier protection and/or spermicidal gel during sexual intercourse and avoiding the following high risk epidemiological factors.(4)

Cigarette Smoking

High Parity

Long-term use of oral contraceptives (>5 Years)

Secondary Prevention :

Screening via Gynecologic Examinations and Cytologic Screening

Precancerous condition have no symptoms and is discovered on routine screening tests & usually diagnosed on colposcopic directed biopsy examination.(7)

Regular gynecologic examinations

Cytologic test (Papanicolaou smear)

HPV DNA Testing

In low resource settings the following alternative approaches of VIA & VILI can be implemented effectively where Pap Test is not feasible for the mass screening because of the lack of trained manpower, infrastructure, quality assurance & the cost involved (8)

Visual Inspection of cervix with Acetic Acid (VIA)

VILI (Visual Inspection of cervix with Lugol's Iodine)

Secondary prevention : Treatment of the premalignant cervical lesions.

Estimates from population studies in the developed countries suggest that screening using the Pap Test may decrease cancer incidence and mortality by more than 80%.(9)

V) Optimal Diagnostic Criteria, Investigations, Treatment & Referral criteria

Situation 1 : At Secondary Hospital / Non- Metro situation : Optimal Standards of treatment in situations where technology and resources are limited.

a)Diagnostic criteria :

History

Physical Examination & gynaecological examination including Per Vaginal & Per Rectal Examination.

**Definitive Diagnosis : On histopathology of cervical growth/ lesion biopsy either punch / knife / Colposcopic Biopsy / Endocervical curettage / Diagnostic LEEP
Cone biopsy (indicated for diagnosis of microinvasive cervical cancer)**

b) Investigations :

Histopathology/ Pathologic review

Blood : Hb%, CBC, KFT, LFT, Blood Sugar F & PP, HbsAg, HIV

Imaging :

X-ray Chest,

USG Whole abdomen & TVS (For Measuring the tumor size) or

CECT/ MRI Whole abdomen when facility exists / IVP (Clinically Parametrial involvement is suspected and the CT facility is not available)

EUA, Cystoscopy / Sigmoidoscopy when parametrial / bladder / rectal involvement is suspected.

Other Investigations if required based on comorbid conditions.

c) Cancer Cervix is staged as per the FIGO Staging 2009(9)

Carcinoma of the cervix uteri.

Stage I : The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

IA Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm

IA1 Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm

IA2 Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm

IB Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA ☐

IB1 Clinically visible lesion ≤ 4.0 cm in greatest dimension

IB2 Clinically visible lesion >4.0 cm in greatest dimension

Stage II Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

IIA Without parametrial invasion

IIA1 Clinically visible lesion ≤ 4.0 cm in greatest dimension

IIA2 Clinically visible lesion >4 cm in greatest dimension

IIB With obvious parametrial invasion

Stage III The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney ☐☐

IIIA Tumor involves lower third of the vagina, with no extension to the pelvic wall

IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

Stage IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV

IVA Spread of the growth to adjacent organs

IVB Spread to distant organs

☐ All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with “early (minimal) stromal invasion” (~1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.
On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

d) Treatment : Is decided based on the FIGO staging of the cervical cancer . (As described with the situation 2)

Standard Operative procedures :

Inpatient :

Type I Hysterectomy with or without Salpingo oophorectomy
Trachelectomy
Type II / III Radical hysterectomy with or without Salpingo oophoprectomy & Pelvic lymphadenectomy

Outpatient : Biopsy / ECC / Colposcopy / Diagnostic LEEP Cervix

Day Care : EUA / Cone Biopsy ./ LEEP Cervix (Loop Eletric excision procedure) & Cystoscopy/ Sigmoidoscopy.

Referral Criteria :

Diagnosed cases of cervical cancer should preferably be referred to Regional Cancer Centre / Nearest Cancer centre / Hospital with facility of Radiation Therapy / Gynae Cancer Surgery

Suspicious cases with diagnostic dilemma.

Young patients with the diagnosis of early stage cervical cancer who opt for fertility preserving surgery.

Situation 2: At superspaeciality Facility in Metro location where higher – end technology is available.

a)Diagnostic criteria : are similar to that in Situation 1.

History

Complete Physical examination, Gynaecological examination including Per Vaginal & Per Rectal Examination.

Definitive Diagnosis :

On histopathology of cervical growth biopsy / endocervical biopsy / Endocervical curettage / Cone Biopsy Cervix / Diagnostic LEEP Cervix

b) Investigations

Histopathology / Pathologic review

Blood : Hb%, CBC, KFT, LFT, Blood Sugar F & PP, HbsAg, HIV

Imaging : X-ray Chest, CECT/ PET CT (Optional)/ MRI

EUA,Optional in stage IB2 and greater / doubtful parametrial involvement.

Cystoscopy /Sigmoidoscopy when bladder/ bowel involvement is suspected.

Other investigations required for the co- morbid conditions.

c) Cervical Cancer is staged as per the FIGO 2009 Criteria.

Treatment

PRIMARY TREATMENT DEPENDING ON THE CLINICAL STAGE of the disease.

In early stage of the disease, stage IB & IIA similar cure rates are achieved with either primary surgery or radiation therapeutic treatment. The choice between the primary surgical or radiotherapeutic treatment depends on the age of the patient, co- morbid conditions, facilities & expertise available.(10)

Stage IA1

- Extrafascial hysterectomy

or

- Observe if patient desires fertility or if inoperable (11)
(only if cone biopsy has negative margins & no LVSI)

or

- **Modified radical hysterectomy or trachelectomy**
+ pelvic lymph node dissection if lymphovascular invasion

Or

ICRT when unfit for Surgery (12)

Dose 10,000 – 12,500 cGy at vaginal surface

Stage IA2

- **Modified Radical hysterectomy (Type II) +pelvic lymph node dissection**
+/- para aortic lymph node sampling (13)

or

- **Brachytherapy +/- pelvic RT(total point A dose : 75-80 Gy)**

or

- **Radical trachelectomy + pelvic lymph node dissection**
+/- paraaortic lymph node sampling.(14)

Stage IB1 & IIA1

- **Radical hysterectomy + pelvic lymph node dissection**
+/- paraaortic lymph node sampling (category 1)(5)

or

- **Pelvic RT + brachytherapy (total point A dose : 80-85Gy)**

or

- **Radical trachelectomy for tumors</= 2cm (Stage IB1)(14)**
+pelvic lymph node dissection +/- paraaortic lymph node sampling.

Laprosopic Surgery: The role of minimal access surgery in management of cervical cancer is evolving at present. Presently, laparoscopic radical hysterectomy with pelvic lymphadenectomy can be offered to patients with stage IB1 cervical cancer as an alternative to the open abdominal radical hysterectomy in suitable patients with a low BMI and no major co-morbid conditions. For optimizing results of the procedure, it should be done only by surgeons trained in the application of advanced laparoscopic surgery to gynecological cancer management and in specialized cancer centres with a large volume gynecologic oncological

Stage IB2 & Stage IIA2

Treatment options

- **Pelvic RT + concurrent cisplatin containing chemotherapy**
+ brachytherapy (total point A dose >/= 85Gy(category 1)(15,16)

or

- **Radical Hysterectomy + pelvic lymph node dissection**

+ paraaortic lymph node sampling (category 2B)

or

• Pelvic RT + concurrent cisplatin containing chemotherapy

+ brachytherapy (total point A dose 75-80Gy)

adjuvant hysterectomy (category 3)(15)

Histopathology

Tumor size, type, Grade, Lymphovascular space involvement, involvement of vagina, microinvasion of the parametrium, Number of nodes dissected, Number of positive nodes. Involvement of the Endometrium/ tubes/ ovaries or any coexisting pathology

ADJUVANT TREATMENT DEPENDING ON SURGICAL FINDINGS

➤ Negative Nodes

1. Pelvic RT if combination of high risk factors (category 1)

(ie large primary tumor ,deep stromal invasion ,and/or lymphovascular space invasion)(17)

2. No above risk factors : Observe

➤ Positive Pelvic nodes and/or Positive surgical margin and /or Positive parametrium

1. Pelvic RT + concurrent cisplatin containing chemotherapy

(category 1)(18)

+/- vaginal brachytherapy.

➤ Paraaortic lymph node positive by surgical staging

A. Chest CT / PET CT scan Negative

Paraaortic lymph node RT + concurrent cisplatin containing chemotherapy

+ Pelvic RT +/- brachytherapy.

B. Chest CT / PET CT Scan Positive for distant metastases

1. Suspicious Areas Biopsy Negative

• Paraaortic lymph node RT + concurrent cisplatin containing chemotherapy

+ Pelvic RT +/- brachytherapy

2. Suspicious Areas Biopsy Positive

▪ Systemic therapy +/- individualized RT.

PRIMARY TREATMENT DEPENDING ON THE CLINICAL STAGE

Stage IB2, Stage IIA2, Stage IIB, IIIA ,IIIB ,IVA

A. Radiological Imaging CT/ MRI / PET(19,20)

A1. Negative Adenopathy : Pelvic RT + concurrent cisplatin containing chemotherapy + brachytherapy.

A2. Positive Adenopathy : Consider needle Biopsy.

B. Surgical staging : Extraperitoneal or laparoscopic lymph node dissection (category 2 B)(21)

B1. Para aortic Nodes Negative : Pelvic RT + concurrent cisplatin containing chemotherapy (category 1)+ brachytherapy.

B2. Para aortic nodes Positive : See node status.

Stage IB2, Stage IIA2, Stage IIB, IIIA ,IIIB ,IVA Node Status

A. Pelvic lymph node positive & Paraaortic lymph node negative by surgical staging

Pelvic RT + concurrent cisplatin containing chemotherapy (category 1)+ brachytherapy.

B. Paraaortic lymph node positive by surgical staging

B1. Further radiologic workup negative for distant metastases:

Pelvic RT + paraaortic lymph node RT +concurrent cisplatin containing chemotherapy + brachytherapy.

B2. Further radiologic workup positive for distant metastases:Consider Biopsy of suspicious areas.

If Biopsy Negative:

Pelvic RT + paraaortic lymph node RT + concurrent cisplatin containing chemotherapy + brachytherapy.

If Biopsy positive:

Systemic therapy +/- Individualized RT.

SURVEILLANCE

- Interval H& P.
- Cervical / vaginal cytology every 3-6 months for 2 yrs,then every 6 months for 3-5 yrs,then annually.
- Chest X Ray annually (optional)

- CBC, BUN, creatinine every 6 months (optional)
- PET CT scan as clinically indicated.
- Recommended use of vaginal dilator after RT.
- Patient education regarding symptoms.

Standard Operating Procedure

Inpatient : All major / radical surgical Procedures

Type I Hysterectomy with or without bilateral salpingo oophorectomy

Type II / Type III Radical Hysterectomy with or without salpingo oophorectomy with Pelvic Lymphadenectomy.

Radical hysterectomy (type III) and bilateral pelvic lymphadenectomy involves removal of entire uterus, upper third vagina, bilateral parametria, uterosacral, utero-vesical ligaments and bilateral pelvic lymph nodes. Bilateral salpingo-oophorectomy is discretionary.

Radical trachelectomy

Para aortic Lymphadenectomy / Sampling

Outpatient : Colposcopy Biopsy, ECC, Diagnostic LEEP Cervix.

Day Care : EUA & Cystoscopy, Rectosigmoidoscopy, Cone Biopsy

Referral Criteria :

On diagnosis of the cervical cancer on histopathology.

Young women with early stage ca cx opting for the fertility preserving surgery the patient should be referred to the Gynae Oncology, Tertiary Cancer centre.

Who does what? And Timelines

Doctor :

Specialist : Primarily should be seen by Gynae Oncologist / Gynaecologist trained in oncology for at least 1 year in prestigious cancer centre.

Diagnosis

Workup

Clinical Staging

Treatment plan in multidisciplinary tumor board

Primary surgery / Radiationtherapy / Concurrent chemo radiation therapy

Average time from diagnosis to execution of the treatment should be 2-3 weeks.

**Nurse : Counseling
To Implement orders
Onco nursing
Doctor patient co-ordination**

**Technician:
Technical Inputs of respective field.
Radiotherapy technician
Operating theatre technician**

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CARCINOMA ESOPHAGUS

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CASE DEFINITION

Carcinoma Esophagus is the commonest cancer in Asian belt along China, Kazhakistan (endemic zone) .It is associated with poor socioeconomic status, nutritional deficiencies, smoking, alcohol and tobacco intake and eating of pickled food. H Pylori infection, hiatus hernia and GERD are predisposing factors for carcinoma esophagus. In India it is most common in North East and constitutes 3-10 % of all malignancies in various regions/States

WHEN TO SUSPECT

Presenting Symptoms

Most common presenting feature of carcinoma esophagus is dysphagia, initially to solids and then to liquids. Other symptoms that patient may present with are

- Odynophagia
- Features of GERD
- Dyspepsia
- Loss of weight
- Anorexia
- Left supraclavicular node
- Haematemesis
- Vomiting

Differential Diagnosis

All elderly patients presenting with long standing dyspepsia and features of GERD or with anorexia, loss of weight and dysphagia,should be investigated for carcinoma esophagus
Common differential diagnosis are

- GERD
- Achlasia cardia
- Hiatus Hernia
- Esophageal diverticulum or stricture

Examination

Besides the routine general and systemic examination, patient should be assessed for

- General condition
- Nutritional status
- Pallor
- Left supraclavicular node

WORKUP FOR DIAGNOSIS AND STAGING

Investigations-

Following investigations are mandatory for assessing any suspected or diagnosed case of Carcinoma Esophagus

- Upper GI Endoscopy –To see for
 - Presence of growth
 - Site of growth
 - Nature of growth
 - Vertical and circumferential extent of growth
 - Passage of scope beyond the growth
 - Status of stomach
 - Presence of Barrets esophagus
(Naso gastric feeding tube to be placed if esophageal lumen found to be obstructed)
- Endoscopic Biopsy- from representative site. Following to be assessed
 - Histology
 - Differentiation
 - Presence of Barrets
- CECT Chest and upper abdomen-To see for
 - Vertical and Horizontal extent of diseases
 - Adherence or infiltration of surrounding structures like trachea, main bronchus, aorta and pericardium
 - Para esophageal nodes
 - Involvement of GE Junction and proximal stomach in the lower third esophageal and GEJunction cancers
 - Liver metastasis
 - Pericardial and plural effusion
 - Ascitis
 - Perigastric lymphnodes
- FNAB of left supraclavicular node if present and left scalene pad of fat biopsy if nodularity felt
- Hb, TLC, DLC, blood grouping
- Biochemistry-LFT,RFT, Blood Sugar, Electrolytes and platelets
- ECG
- Ba Swallow-for lower third and GE Junction tumors
- Bronchoscopy for Upper and middle third carcinoma esophagus

Optinal Investigations

Following Investigations are optional and may be done in tertiary care centres where facilities are available

- Endoscopic Ultrasound
- Endoscopic ultrasonographic FNAB of paraesophageal nodes
- PET Scan
- Her 2 Ney receptor study by FISH technique on biopsy specimen

STAGING (AJCC 7th Ed 2010)

- **Tis** High grade dysplasia (ca in situ)
- **T1a** Tumour invades lamina propria or muscularis mucosa
- **T1b** Tumour invades submucosa
- **T2** Tumour invades muscularis propria
- **T3** Tumour invades adventitia
- **T4a** Resectable tumour invading pleura, pericardium or diaphragm
- **T4b** Unresectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea etc
- **Nx** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1-2 regional lymph nodes
- **N2** Metastasis in 3-6 lymph nodes
- **N3** Metastasis in seven or more regional lymph nodes
- **M0** No Metastasis
- **M1** Distant Metastasis

Group staging

	Stage	T	N	M
•	0	T1	N0	M0
•	1A	T1	N0	M0(G1,2)
•	1B	T1	N0	M0(G3)
•		T2	N0	M0(G1,2)
•	IIA	T2	N0	M0(G3)

•	IIB	T3	N0	M0
•		T1-2	N1	M0
•	IIIA	T1-2	N2	M0
•		T3	N1	M0
•		T4a	N0	M0
•	IIIB	T3	N2	M0
•	IIIC	T4a	N1-2	M0
•		T4b	any	M0
•		any	N3	M0
•	IV	any	any	M1

Pathology

Almost 95% cancers of the Esophagus are Squamous cell carcinomas (excluding GE Junctions carcinomas) and the remaining may be Adenocarcinoma, soft tissue sarcoma, GIST and benign soft tissue tumors

TREATMENT

Neoadjuvant Therapy-All patients with growths T2N0 and beyond should receive Neoadjuvant Chemoradiation with 5000Gy of radiotherapy with weekly Cis/Carbo platin and 5 Fu. Chemotherapy with two drug regime of any combination including platinum and taxane based drugs can be used too

Surgery-Surgery remains the gold standard in treatment of carcinoma esophagus

Since Surgery involves thoracic surgery and post operative critical care, treatment of esophageal malignancies should be undertaken where facilities and expertise for thoracic surgery and critical care are available

Contraindications to Resection-Surgical resection should not be considered in the following circumstances

- T4b lesion
- Left supra-clavicular node
- Distant metastasis
- Multi-station bulky nodal mass
- Poor general condition

- Co-morbid medical conditions making patient unfit for anaesthesia

Carcinomas of the cervical esophagus should be treated with Concomitant Chemo and Radio Therapy (CCRT)

Treatment of Squamous Cell carcinoma Esophagus

Preoperative Laprotomy can be done to asses operability

Total Esophagectomy with two field nodal dissection is the preferred surgery for carcinoma esophagus.

This includes the removal of complete esophagus, removal of paraesophageal lymphnodes and D2 dissection of gastric lymphnodes, and using a stomach tube as conduit to restore continuity with anastomosis in the left side of the neck. This can be done by following two procedures

- Transthoracic Total Esophagectomy (TTE), which includes a right posterolateral thoracotomy for mobilization of esophagus and paraesophageal nodal dissection ,mobilization of stomach with D2 nodal dissection of gastric lymph nodes ,total esophagectomy, gastric mobilization and formation of gastric tube through a upper midline laparotomy incision and pulling up the gastric tube and anastomosing with proximal esophagus in the left side of the neck.A minimum of 15 nodes should be dissected for adequate nodal dissection.Mobilisation of the esophagus can also be done by **VATS(Video Assisted Thoracic Surgery)**
- Transhiatal Total esophagectomy(THE) -Is a two step procedure where the thoracotomy is excluded and the esophagus is mobilized blindly thorough transehiatal route.Adequate paraesophageal nodal dissection is not possible through this procedure,however it avoids a thoracotomy.Being a blind procedure Transhiatal Total esophagectomy should be undertakem,preferably only for cancers of the lower third esophagus.

Partial Esophagectomy (Ivor-Lewis Procedure)

This procedure is performed for cancers of the lower third esophagus with a right thoracotomy and upper midline laparotomy incision. The lower third of esophagus is excised with a margin of 5 cms and anastomosis done with the gastric tube is done in the mediastinum.Mobolization of stomach,formation of gastric tube and nodal dissection remain the same as for total esophagectomy

Management of Carcinoma Esophagus in special situations

Early Carcinoma esophagus-It is rare to find early cases of cancer esophagus in india,however small T1 lesion scan be treated by any of the following procedures

- Endoscopic mucosal resection
- Endoscopic submucosal resection
- Radiofrequency ablation
- Photodynamic therapy

- Cryotherapy
- Local excision

GE Junction Cancers-Squamous Cell carcinoma of GE Junction-should be treated as Carcinoma esophagus with partial or total esophagectomy

Involvement of proximal Stomach-Squamous cell carcinomas of GEJunction or lower third esophagus rarely involve proximal stomach, but if they do then surgical procedure will depend on the extent of involvement. If there is minimal involvement and adequate margin can be obtained and adequate length of the gastric tube can be formed then proximal gastrectomy can be performed with total esophagectomy.

Histopathological Examination-Operative specimen should be examined for the following

- Histology
- Grade
- Margins
- Depth of invasion
- Involvement of extra esophageal tissue
- Lymphovascular invasion
- Number of nodes dissected
- Number of nodes involved
- Perinodal & Perineural infiltration
- Her-2 Neu by FISH in metastatic disease

Adjuvant therapy-

R0 resection-Observe (Note 1. Cases where less than 15 nodes are dissected, can be treated as

R1 Resection 2, nodal Status cannot be adequately assessed after THE or Partial esophagectomy)

R1/R2 Resection-CCRT

Management of Adenocarcinoma Esophagus- The Surgical management of adenocarcinoma Esophagus is same as that of Squamous cell carcinoma but Neoadjuvant and adjuvant therapy differs and is as follows

Neoadjuvant therapy-All patients with growths T2N0 and beyond should receive four cycles of chemotherapy with two drug regime of any combination including platinum and taxane based drugs

Adjuvant therapy

R0 RESECTION

- NO PREOP THERAPY
 - T1,T2,N0 ,OBSERVE
 - T3 /N+, CCRT

- AFTER NACT
 - T2NO, CHEMOTHERAPY
 - T3 /N+ CCRT

R1/R2 RESECTION CCRT

Management of other malignancies of esophagus-Soft Tissue sarcomas and GIST of esophagus are to be treated with total esophagectomy without nodal dissection.Chemotherapy in these cases chemotherapy would be same as that for soft tissue sarcomas and GIST of the rest of GI Tract.Benign tumors can be managed with excision .

Management of Unresectable tumors or of patients with poor performance status

Definitive CCRT-Concurrent Radiotherapy with 6000Gy of radiotherapy with either of the following combination of drugs.

- Cisplatin and 5FU

- Paclitaxel/Docetaxel with 5FU

Management of Metastatic disease- Metastatic disease is managed with single or two drug regime using chemotherapy platinum,taxanes and 5-FU or supportive care. TRANSTUZUMAB (Herceptine)can be used for HER2 neu + cases

Paliative Care

Esophageal obstruction

- Endoscopic lumen restoration

- Laser excision

- Endoscopic lumen enhancement
 - Expandable stents
 - Wire guided balloon dilatation

- Surgical placement of gastrostomy or jejunostomy tube

- External Beam Radiotherapy

- Palliative Chemotherapy

BLEEDING

- Endoscopic intervention

- EBRT

PAIN

- Local blocks
- Painkillers

TRACHEO ESOPHAGEAL FISTULA

- Stenting

FOLLOWUP

All patients of Carcinoma esophagus to be followed regularly after completion of treatment, to look for

- Anastamotic Stricture
- Anastamotic recurrence
- Local recurrence
- Nodal recurrence
- Distant Metastasis (Liver and lung)

Frequency of follow-up-Once in every three months for two years and then six monthly till five years post treatment, followed by annual review, lifelong

Following Investigation sto be done at Review

- Hb,TLC,DLC
- LFT
- X-ray chest
- USG Abdomen
- UGI Scopy ,once in a year
- CECT Chest(Optioanl,without any symptoms)

Prevention

- Decrease use of tobacco,alcohol and stop smoking
- Minimal or no use of poorly preserved,pickled and smoked food
- Improve hygiene
- Treat GERD

FLOWCHART

Squamous Cell Carcinoma & Adenocarcinoam

Tis ----- Endoscopic Mucosal Resection/Ablation

T1a-----Endoscopic Mucosal Resection/Ablation OR Esophagectomy

T1b-----Esophgectomy

Squamous Cell

T2,3,4 N0,1,2,3-----Neoadjuvant CCRT-----Esophagectomy

Post esophagectomy-----R0-----Observe

R1/2-----CCRT

AdenoCarcinoma

T2,3,4 NO,1,2,3-----Neoadjuvant Chemotherapy-----Esophagectomy

Post esophagectomy-----

R0 RESECTION

- NO PREOP THERAPY
 - T1,T2,NO ,OBSERVE
 - T3 /N+, CCRT

- AFTER NACT
 - T2NO, CHEMOTHERAPY
 - T3 /N+ CCRT

R1/R2 RESECTION----- CCRT

Poor Performance status-----Definitive CCRT

Metastatic Disease/recurrence-----Chemotherapy or Supportive care

REFERANCES

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Esophageal cancer

WHEN TO SUSPECT

Presenting Symptoms

Most common presenting feature of esophageal cancer is dysphagia, initially to solids and then to liquids. Other symptoms that patient may present with are

- Odynophagia
- Dyspepsia
- Loss of weight
- Anorexia
- Left supraclavicular node
- Haematemesis
- Vomiting

Investigations

Diagnostic Investigations

1. Barium Swallow (optional) : This continues to be the first investigation in majority of patients presenting with dysphagia. It gives information regarding the 1. Site 2. length of lesion 3. Morphology (Proliferative/Strictureous/ulcerative or combination) 4. Extra esophageal spread (axis deviation, sinuses and fistulation)
2. Esophagoscopy : Fiberoptic esophagoscopy is essential for biopsy/cytology.

Staging Investigations

1. CT scan : Chest and upper abdomen
2. Endoscopic ultrasonography (EUS)
3. Fiberoptic bronchoscopy : for tumours located at and above the level of the carina

CT scan and EUS are complimentary for assessing the lateral extension of disease and lymph node status. EUS scores over CT scan in assessment of the depth of tumour invasion, particularly in early cancer, and status of regional lymph node. However, in strictureous lesions, EUS may not always be possible. CT scan is equally accurate in assessment of T3/T4 lesions; abdominal CT scan additionally can screen liver and coeliac lymph nodes. Bronchoscopy is an essential non invasive investigation for assessing the tracheo-bronchial tree for early or frank invasion. It is recommended prior to surgery or radiation for upper and mid esophageal disease.

PET scan can effectively detect presence of disseminated disease. However, presently it is an investigational modality of investigation. Thoracoscopy and laparoscopy for staging has been investigated and reported increased rate of detecting positive lymph nodes than non invasive staging modalities (Level IIb).

Routine Investigations for assessing fitness for treatment

1. Hemogram
2. Liver Function Test/Renal Function Test
3. Chest X-ray
4. Pulmonary Function Test
5. ECG

Treatment Options

Two factors determine the treatment:

1. General condition or the Performance status
2. Stage

1. General condition or performance status is an important factor in determining the treatment of a patient with cancer oesophagus. Dysphagia, particularly if it is long standing and complete, leads to chronic dehydration and malnutrition. Such patients will not tolerate surgery, radiation or chemotherapy. Supportive care to optimise general condition should be the priority. Subsequently, if performance status improves, definitive treatment can be contemplated depending on stage of the disease.

2. Stage : Patients with localized disease are ideally treated with surgery in the absence of medical contraindications. As per the staging, presence of abdominal or celiac lymph nodes is classified as disseminated disease. However prognosis of patients with abdominal or celiac lymph node metastasis is not the same as that with systemic distant metastasis. Hence, patients with operable local disease should be offered surgery with appropriate lymphadenectomy.

- The preferred treatment of carcinoma of the cervical oesophagus is radical radiotherapy or concomitant chemoradiotherapy

Stage 0 (TisN0M0)

Patients are rarely diagnosed in this stage. The treatment of choice is surgery. If the disease is localised (preferably T1a), Endoscopic mucosal resection (EMR) can be offered in centres with expertise provided the patient is reliable for followup. For more extensive disease, esophagectomy is the treatment of choice.

Stage I (T1N0M0)

Surgery is the treatment of choice. Radiation therapy may be offered if the patient is medically unfit or not willing for surgery.

Stage II/III (T2N0M0, T3N0M0, T1N1M0, T2N1M0)

Surgery for T2 and T3 lesions

Surgery for T4 lesions with limited infiltration of pleura or pericardium which is amenable to complete resection

Neo adjuvant chemotherapy/concomitant chemo-radiation for T3/T4 tumours which are bulky or of doubtful resectability. If there is complete or partial response to neo adjuvant therapy and tumour appears resectable patient should proceed for surgery; if the response is sub optimal and disease appears non resectable, patient should either proceed for radiation or palliative therapy (see below).

Investigational treatments

1. Chemoradiotherapy alone or chemoradiotherapy followed by surgery
2. Neo adjuvant Chemotherapy followed by surgery
3. Post operative radiation therapy

Stage IVa (ant T, any N, M1a)

Surgery (per primum or following neo adjuvant therapy): If the disease is operable in the absence of distant metastases. However, more than 50% of patients will have distant metastases. Such patients will be candidates for palliative treatment.

Principles of Surgery

Surgical Approach

1. Esophago-gastrectomy through left thoraco-abdominal approach (Garlock procedure) : for adenocarcinoma of the cardio-esophageal junction.
2. Trans thoracic esophagectomy with intrathoracic anastomosis (Ivor Lewis procedure).
3. Trans thoracic total esophagectomy with cervical anastomosis.
4. Trans hiatal esophagectomy with cervical anastomosis.

Adenocarcinoma of the cardio-esophageal junction can be resected through a left thoracoabdominal approach. Surgery involves mobilization of the oesophagus upto the inferior pulmonary vein along with dissection of lower paraesophageal lymph nodes, standard mobilization of stomach along with D2 lymphadenectomy. Gastro-oesophageal anastomoses could be either mechanical (using stapler) or hand sewn.

Adenocarcinoma of the distal portion of the oesophagus or cardio-esophageal junction extending into the lower oesophagus where the proximal extent of the tumour is such that adequate margin is not possible through the left thoraco-abdominal approach should be treated by either trans thoracic or trans hiatal esophagectomy. Phase III trial comparing transhiatal esophagectomy to transthoracic esophagectomy and lymphadenectomy for adenocarcinoma of the oesophagus did not find difference in median overall and disease free survival between the two procedures. However, there was a trend towards superior long term (5-year) survival, not reaching statistical significance, in favour of transthoracic esophagectomy (Level Ib).

Carcinoma of the lower, mid and upper esophagus (excluding cervical oesophagus) is managed either by transhiatal or trans thoracic esophagectomy and esophago-gastric anastomosis in the neck or thorax. There is no consensus as to the best or the ideal surgical approach.

Transthoracic esophagectomy has the advantage of mobilization of the oesophagus under vision. Also, systematic mediastinal lymph node dissection can be performed. Trans hiatal approach, according to proponents, is less morbid with fewer pulmonary complications. There are four published Phase three trials comparing the two approaches. Three of these had few patients and thus, meaningful conclusions cannot be drawn. The fourth and the latest trial has 220 patients, all adenocarcinoma restricted to the distal oesophagus or cardio-esophageal junction. There was no difference in the median overall survival; however, there was a trend towards a survival benefit at five years with the trans thoracic approach (Level Ib). The published meta analysis of over 60 trials (both prospective and retrospective) comparing transhiatal to transthoracic esophagectomy did not find any difference in the overall survival (Level IIc). Till results of large randomized trials are available the preferred surgical approach will continue to be biased by surgeons' choice.

Extent of lymphadenectomy

Lymph node metastasis is one of the most important prognostic factors for carcinoma of the oesophagus. Since the oesophagus has extensive lymphatic network and most patients present with advanced disease, the majority of patients undergoing surgery have lymph node metastases. Three field lymph node dissection (lower cervical, mediastinal and abdominal) is reported to improve survival without increased procedure related morbidity and mortality (Level IIa). However, most reported studies are small or have compared results with historical controls. The only one randomized trial of over 60 patients has reported higher, though not statistically significant, survival in patients undergoing three field lymph node dissections (Level Ib). Extensive lymph node dissection provides 'accurate nodal staging' resulting in stage migration and apparent 'improvement in survival'. In absence of conclusive Level I evidence, the advantage of three field lymph node dissection over the conventional limited lymph node dissection remains speculative. In fact, an adequately powered randomized trial could answer the question regarding the importance of lymph node dissection in management of carcinoma oesophagus and indirectly address the issue of transhiatal versus transthoracic approach.

Definitive radiation and chemo-radiation therapy

Two published (RTOG and ECOG) randomized trials have reported better overall survival with concomitant chemo-radiation than radiation therapy alone. However, increasing the dose of radiation therapy (50.4 versus 64.8) in concomitant setting did not result in increased survival (Inter Group trial). Meta analysis of 13 trials combining radiation with chemotherapy published in the Cochrane library has reported an absolute reduction in the mortality and local recurrence rate of 7% and 12% respectively in favour of combination therapy. The combination treatment is associated with increased life threatening toxicities (Level Ia). There are no trials comparing concomitant chemo-radiation with surgery alone. However two trials comparing surgery to radiation alone have reported better survival with surgery (Level Ib). Hence based on the available evidence, if a patient is to be treated with definitive radiation, it should be combined with chemotherapy, provided performance status is optimal.

Surgery as adjuvant to radiation, chemotherapy or combination of both

Pre-operative radiotherapy

A meta analysis as well as the five published randomized trials comparing preoperative radiation therapy to surgery alone have not shown benefit of pre operative radiation over surgery alone (Level Ia).

Pre-operative concomitant chemo-radiation

There are eleven major trials and three meta analysis comparing preoperative concomitant chemoradiation to surgery alone. Meta analysis of pre operative chemoradiation and surgery to surgery alone has reported improved survival and reduced loco-regional recurrence (Level Ia). However, combination treatment is associated with trend towards increased treatment related morbidity and mortality. In the absence of results from a large trial and increased treatment related morbidity, neo adjuvant chemo-radiation should be considered as one of the options of treating localized disease.

Pre-operative chemotherapy

There are nine major published trials of pre-operative chemotherapy in the management of carcinoma of the oesophagus. The two large trials have reported results which are divergent. The Intergroup trial of 440 patients reported by Kelsen et al observed no improvement in survival with pre operative combination of cisplatin and fluorouracil among patients with adenocarcinoma or epidermoid carcinoma of the oesophagus. The MRC trial of 802 patients reported improved survival with two cycles of cisplatin and fluorouracil without additional serious events. The meta analysis of all trials put together concludes that preoperative chemotherapy plus surgery appears to offer a survival advantage at 3, 4, and 5 years, which reached significance only at 5 years compared to surgery alone for resectable thoracic esophageal cancer of any histologic type. The number needed to treat for one extra survivor at five years is eleven patients. (Level Ia).

Post-operative radiotherapy

Three trials have compared surgery and post operative radiation to surgery alone. The Chinese trial of 495 patients observed improved 5-year survival in patients with positive lymph nodes and stage III disease receiving post operative radiation. However, the difference in the overall survival between the two groups was statistically not different. The meta analysis of all three trials also does not show benefit of post operative radiotherapy. Therefore, in the absence of Level I evidence post operative radiotherapy is indicated only for patients with positive margin and residual disease.

Post operative chemotherapy

Phase III trials of surgery and post operative chemotherapy have not reported survival benefit over surgery alone. A Phase III study by Japanese Clinical Oncology Group (JCOG) reported better disease free survival at 5-year with post operative chemotherapy; however there was no difference in the overall survival (Level Ia).In adenocarcinoma of the cardio oesophageal

junction (and stomach) two trials – the MAGIC trial evaluating perioperative chemotherapy with three cycles of ECF given pre as well as 3 cycles given postoperatively, and the MacDonald post operative chemo-radiotherapy trial – both showed improved overall survival (Level Ib). Thus in patients with adenocarcinoma of the cardia having good performance status, perioperative chemotherapy (3 preoperative cycles of ECF and 3 postoperative cycles of ECF) or post operative chemo-radiation should be the standard of care.

Principles of Radiation therapy

Radical radiotherapy

The inclusion criteria are :

- All lesions (except stenotic) in upper / mid / lower esophagus
- Lesion \leq than 5 cm on barium swallow and esophagoscopy
- Histologically proven esophageal carcinoma
- Karnofsky Performance Status (KPS) of $> 60\%$
- Age \leq 60 years.
- Metastatic work - up negative (No palpable S/C nodes, Bronchoscopy & USG abdomen normal).

- External beam radiotherapy (EBRT) alone

Dose : 60 - 64.8Gy / 33 - 36 fractions, with reducing fields

Portal design :

Extended field: esophageal lesion including the lymph drainage areas, with 5 cm margin on either side upto 39.6Gy / 22 fractions/ 4.5 weeks

Reduced fields/ boost: Lesion with 2 - 3 cm. margins, with oblique portals, upto 60 - 64.8Gy / 33 - 36 fractions

- External beam radiotherapy and brachytherapy

When feasible, external Radiotherapy can be combined with Intraluminal radiotherapy (ILRT) as a boost.

Dose of EBRT : 50.4Gy / 28 fractions with reducing fields.

ILRT Boost : 5 - 8Gy / 2-3 fractions high dose rate (HDR), one week apart or single fraction 20Gy low dose rate (LDR).

Concomitant chemo-radiation regimen

- 50Gy in 25 fractions over 5 weeks, plus cisplatin intravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil, 1g/m² per day by continuous infusion on the first 4 days of weeks 1, 5, 8, and 11. (RTOG regimen)

- 60Gy in 6 to 6 1/2 weeks. Chemotherapy to be initiated within 24 hours after the commencement of radiation therapy. 5-FU to be delivered by continuous infusion for 96 hours starting on day 2 at the rate of 1000 mg per m² over 24 hours. This regimen of 5-FU to be repeated once again beginning on day 28. Bolus injection of mitomycin C (10 mg per m²) to be administered on day 2 and not to be repeated. The dose of mitomycin C not to exceed 18 mg and the dose of 5-FU not to exceed 1800 mg over a 24-hour period. (ECOG regimen).

Principles of Chemotherapy

Neoadjuvant chemotherapy protocols

- Two 4-day cycles, 3 weeks apart, of cisplatin 80 mg/m² by infusion over 4 h plus fluorouracil 1000 mg/m² daily by continuous infusion for 4 days. (MRC protocol)
- Cisplatin, at a dose of 100 mg per square meter of body-surface area, given as a rapid intravenous infusion after prehydration on day 1. Immediately thereafter, fluorouracil administered at a dose of 1000 mg per square meter as a continuous infusion from day 1 through day 5 (120 hours) of each cycle. The cycle to be repeated beginning on days 29 and 58. Surgery performed two to four weeks after chemotherapy (Intergroup protocol).

Palliative treatment

If the general condition is good,

1. Relief of dysphagia by placement of esophageal stent alone, preferably self expanding metallic stent as these are easy to deploy.
2. Radiation therapy with intubation if associated with significant dysphagia
3. Intraluminal radiation therapy alone.
4. Endoscopic laser destruction of tumour or electrocoagulation.

Palliative radiotherapy

The intent of treatment is to achieve quick and good palliation in the form of relief of dysphagia and pain.

The inclusion criteria are :

- Lesions in upper / mid / lower esophagus
- Lesion \leq 10 cm long on barium swallow and esophagoscopy
- Histologically proven esophageal carcinoma
- Karnofsky performance status (KPS) of \geq 50%
- Recurrent / metastatic disease.

Dose : 3000cGy /10 fractions /2 weeks

Portal : Esophageal lesion with 2-3 cm margin

Evaluation and response assessment is done after 4 - 6 weeks and further external Radiotherapy or Brachytherapy boost may be delivered.

Reduced field / boost : 2000cGy/10# / 2 weeks, using oblique portals

Palliative radiation can also be delivered in the form of ILRT alone or in combination with EBRT. The dose per fraction ranges from 5 - 8Gy, in 2- 3 fractions, one week apart. There is no difference in local control or survival between high dose rate brachytherapy compared with external beam radiation. (Level II)

Investigational Treatment

1. Palliative chemotherapy with intubation if associated with significant dysphagia. Response rates ranging from 30% to 50% and one year survival ranging from 0% to 5% is reported with platinum based combination chemotherapy.

If the general condition is poor with limited life expectancy

1. Nasogastric tube placement for feeding if possible.
2. Supportive care.

Treatment of esophageal fistula

1. Esophageal intubation with stent.
2. Oesophageal and tracheal/bronchial stent placement (double stenting) when possible if the fistula is large or if the tracheal lumen is compromised.

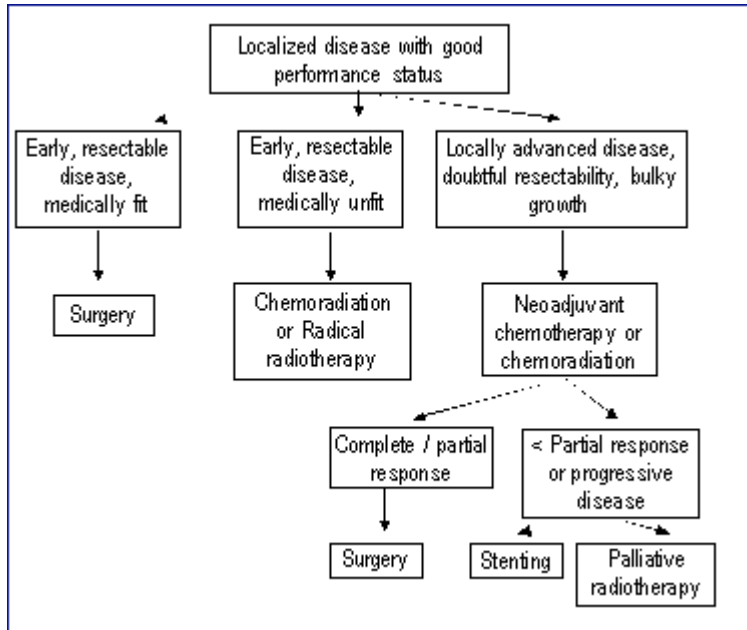
Treatment of Recurrent disease

1. Salvage surgery for localised resectable failures.
2. Palliative treatment or supportive care alone as described before.

Management algorithm for esophageal cancer

Workup

1. Barium swallow (optional)
2. Upper GI scopy with biopsy / cytology
3. CT scan chest and upper abdomen
4. Fiber optic bronchoscopy – for upper and middle third growths
5. Routine hematology, biochemistry
6. Pulmonary function tests – if surgery contemplated
 - a. Assess stage of disease – (i) Localized (ii) Disseminated
 - b. Assess performance and nutritional status



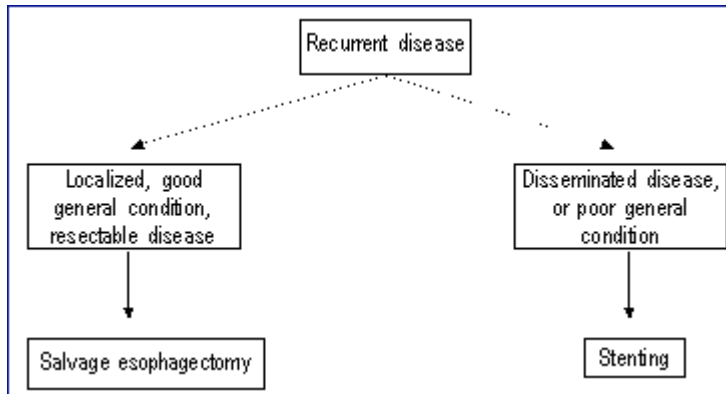
Disseminated disease with good performance status

- Stenting
- Palliative chemotherapy

Poor performance status and / or nutritional status

- Stenting

Recurrent disease



Best supportive care

- Stenting – to relieve obstruction
- Enteral feeding through nasogastric tube or gastrostomy
- Pain relief

NAME OF CONDITION; Gall Bladder cancer

VIII. WHEN TO SUSPECT/ RECOGNIZE?

c) Introduction:

It is the most common biliary tract cancer and is the fifth leading gastrointestinal malignancy in the United States. It produces symptoms late in the course of the disease, disseminates rapidly from the primary site, and responds infrequently to nonsurgical therapy. The overall median survival for all patients is less than 6 months. The disease is up to five times more common in females. It is usually associated with gallstones, although few patients with gallstones actually develop gallbladder cancer

Case definition:

For both situations of care (*mentioned below**)

IX. INCIDENCE OF THE CONDITION IN OUR COUNTRY

The reported crude rate for gallbladder cancer in India is 1/100,000. The comparison of different population based cancer registries indicates that GB cancer varies in different regions. The reported incidence ranged from 10/1, 00, 000 in Delhi to 2-3/1, 00, 0 00 in South India.

X. DIFFERENTIAL DIAGNOSIS

Xanthogranulomatous cholecystitis is a relatively rare inflammatory condition of the gallbladder, requires to be differentiated from GB cancer. Characteristic findings on the CT scan are intramural hypodense nodules. CA 19-9 levels may be normal, and FDG-PET scan may be negative.

Mid bile duct cholangiocarcinoma may simulate a GB cancer and can be differentiated by optimal cholangiography as can Mirizzi syndrome.

XI. PREVENTION AND COUNSELING

There is no way to prevent gallbladder cancer, however its risk may be decreased by maintaining healthy weight, avoiding tobacco and having surgery for high risk conditions such as patients with large stones, porcelain gallbladder, polyps, anomalous pancreatobiliary ductal union, and those belonging to certain races such as Pima Indians.

XII. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

Patients with gallbladder cancer are often initially asymptomatic. Nonspecific symptoms of abdominal pain and weight loss may mimic the symptoms of benign gallbladder disease. Jaundice is an ominous sign in patients with gallbladder cancer and usually indicates advanced disease. A palpable gallbladder may be found on examination.

Ultrasonography is usually the first investigation in suspected gallbladder disease. Findings suggestive of cancer include asymmetric wall thickening, discontinuous mucosa, echogenic mucosa, submucosal echolucency, or mass lesion. Doppler examination may help to assess the blood flow through areas of mucosal abnormalities and also the patency of the regional vasculature (hepatic artery and portal vein)

CT scan is currently the gold standard in imaging of a suspected GB cancer and can show the mass lesion, extension, vascular involvement, nodal disease and metastasis.

Magnetic resonance imaging has the advantage of no radiation plus the opportunity to have a all information in one single investigation that provides cross-sectional images of the tumour, extension, nodal disease , cholangiography and angiography. Laparoscopic evaluation should be considered before proceeding to open resection as up to 55% may have peritoneal secondaries.

Biopsy is not essential for tumours deemed resectable by imaging, however for unresectable disease planned for nonsurgical therapy histologic confirmation is mandatory.

Treatment:

Radical re-resection (after a complete staging including laparoscopy demonstrating resectability) is recommended for patients with incidental gallbladder carcinoma stage T1b (tumour invades muscle layer) or greater. Patients with T1a tumours (tumour invades lamina propria) do not further benefit from re-resection if the gallbladder were removed intact and should be observed only.

Incidentally detected tumours at surgery should be confirmed by frozen section biopsy and full evaluation should be performed using intraoperative ultrasound. Surgery is converted to open resection with en-bloc hepatic resection and lymphadenectomy with or without bile duct resection.

Surgical resection is the only potentially curative treatment for preoperatively diagnosed resectable cancer. Resection is an extended cholecystectomy which includes cholecystectomy, en-bloc hepatic resection and lymphadenectomy (porta hepatis, gastrohepatic ligament, retroduodenal) with or without bile duct excision. Involvement of the interaortocaval node is considered as synonymous of disseminated disease, and if this lymph node is positive at frozen section, curative resection must be abandoned. Bile duct resection is considered for cystic duct lesions or invasion of the bile duct or for clearance of bulky nodes. It may also be indicated when the bile duct is itself involved by tumour. Surgery may also involve

removal of adjacent organs such as the duodenum, colon, stomach, and pancreas to achieve R0 resection, as negative margins is the most important determinant of survival.

Resectable advanced disease diagnosed at surgery may be considered for operative treatment. Biliary enteric bypass, however if diagnosed prior to surgery should be considered for endoscopic or percutaneous biliary drainage.

Adjuvant and palliative chemotherapy has limited role and Gemcitabine based chemotherapy and 5FU based chemo radiation can be considered in patients with good performance status.

***Situation 1: At Secondary Hospital/ Non-Metro situation: Optimal Standards of Treatment in Situations where technology and resources are limited**

IX. Clinical Diagnosis:

Any elderly patient with right upper abdominal pain and weight loss should be evaluated for gallbladder cancer and the diagnosis confirmed by imaging.

When a patient reports with gall stones (symptomatic or asymptomatic), care should be taken in reviewing the clinical history and also the ultrasound examination. If there is asymmetric gall bladder wall thickening, or mass lesion, or jaundice, then the patient needs more extensive evaluation in a tertiary care center. Since the best opportunity for long term cure of patients is in R0 resection (complete resection with negative margins), preoperative definition of tumour extent is critical, and patients must be managed in a tertiary care center.

X. Investigations:

USG, CT, MRI

XI. Treatment:

Cholecystectomy for early lesions.

Chemoradiotherapy

XII. Referral criteria:

All patients for extended cholecystectomy should be referred to specialist centre.

***Situation 2: At Super Specialty Facility in Metro location where higher-end technology is available**

d) Clinical Diagnosis:

Any elderly patient with right upper abdominal pain and weight loss should be evaluated for gallbladder cancer and the diagnosis confirmed by imaging.

e) Investigations:

USG,CT MRI, IOUS,

f) Treatment:

Extended cholecystectomy

Chemoradiotherapy.

Standard Operating procedure

a. In Patient

b. Out Patient

c. Day Care

XIII. WHO DOES WHAT? and TIMELINES

a. Doctor

b. Nurse

c. Technician

XIV. FURTHER READING / REFERENCES

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RESOURCES REQUIRED FOR ONE PATIENT / PROCEDURE (PATIENT WEIGHT 60 KGS)

(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

Situation	HUMAN	INVESTIGATIONS	DRUGS &	EQUIPMENT
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	RESOURCES		CONSUMABLES	
1				
2				

Lung cancer

Introduction

Lung cancer is a major problem in both developed and developing countries in the world. It is the leading type of cancer (more than a million new cases; 12.8% of all cancers) and the leading cause of cancer mortality (921,000 deaths; 17.8% of all cancer deaths) worldwide. It is expected that lung cancer will remain a major health problem at least for the next 30-40 years, even if there is a reduction in incidence as a result of smoking cessation interventions. In India, Untreated, it has a high mortality with 95% patients dying within one year.

Lung cancer is broadly divided into two types – small cell and non-small cell. This general histologic classification reflects the clinical and biological behavior of these distinct tumor types. Small cell lung cancers (SCLC) grow rapidly, metastasize widely and are treated primarily with chemotherapy. Eighty percent of SCLC are metastatic on presentation. Non-small cell lung cancers (NSCLC) are divided into squamous cell cancers, adenocarcinomas and large cell carcinomas. Nearly half of all NSCLC in developed countries (and one fourth of cases in India) are diagnosed in localized or locally advanced stage when they are treated by resection or combined modality treatment with or without surgery.

Smoking is the single most important risk factor for all types of lung cancers. Attempts to reduce lung cancer mortality should therefore primarily be focused on smoking cessation, which has the potential to be the single most important public health intervention to reduce cancer deaths.

Management of NSCLC

I. Patients with localized NSCLC (T1-3, N0-1)

These include patients upto T3N1 NSCLC, i.e., all stage I, II and T3N1 stage IIIA.

Workup includes

1. Chest X-ray
2. CT scan chest and upper abdomen
3. Fiber optic bronchoscopy
4. Cyto/histological diagnosis if possible – sputum cytology, bronchoalveolar lavage/brushings cytology, post bronchoscopy sputum cytology, CT guided biopsy
5. Arterial blood gas analysis
6. Pulmonary function test and diffusion coefficient of carbon monoxide (DLCO)

7. Ventilation-perfusion (V/Q) scan – if pulmonary function tests reveal borderline pulmonary reserve
8. Mediastinoscopy is indicated in patients with T3 and/or N1 tumors
9. Metastatic workup – PET-CT scan, MRI scan brain– indicated in patients with T3 and/or N1 tumors

Note : A cyto/histological diagnosis is preferable but not mandatory prior to surgery.

A complete metastatic workup is indicated in

- a) Patients with T3 and/or N1 tumors
- b) Borderline operative patients (increased risk because of borderline PFT or intercurrent cardiac or other medical illnesses) with early stage disease
- c) Patients with symptoms or signs of distant metastases.

Patients with T1-2, N0 NSCLC with no symptoms of metastatic disease do not require a routine metastatic workup.

**Surgery is the treatment of choice in patients with localized disease with no involvement of mediastinal lymph nodes.
(Level III, Grade B)**

Preoperative Management

1. Smoking cessation
2. Bronchodilators
3. Intermittent Positive Pressure Breathing (IPPB)
4. Chest physiotherapy
5. Antibiotics – only if infection present

Surgical resection – general principles

- Lobectomy or pneumonectomy should be done depending on the extent of disease (provided the patient has adequate pulmonary reserve). One randomized trial (LCSG) and eight non-randomized trials have shown lower survivals with sublobar resections compared to lobectomy. (Level Ib, Grade A)
- Limited resection (segmentectomy, wedge resection) may be done only if pulmonary reserve is inadequate for lobectomy, provided otherwise medically fit for surgery. Reduced survival compared to lobectomy, but better results than radical radiotherapy alone. (Level III, Grade B)
- N1 and N2 lymph nodal resection and mapping (sampling or systematic lymph node dissection) should be done. There is universal consensus that SMLND is a better staging and prognosticator than mediastinal lymph nodal sampling. There is no consensus that SMLND improves survival in patients with NSCLC. Two randomized trials found no difference in survival between mediastinal lymph node sampling and systematic mediastinal lymph node dissection, whereas one randomized and one large

nonrandomized trial found superior survival with systematic mediastinal lymph node dissection. (Level Ib, Grade A)

- Curative (radical) radiotherapy should be given if the patient is medically unfit for surgery. (Level III, Grade B)
- Parenchyma preserving lung resection (sleeve resection, bronchoplasty) is preferred over pneumonectomy if anatomically appropriate and negative margins can be obtained. (Level III, Grade B)

VATS lung resections

Preliminary data from VATS lung resections suggest similar 2-3 year survival outcomes to open surgery but long term outcomes are not yet available. However, most studies of VATS lung resections have had strict selection criteria whereas comparative open surgeries have been an unselected group. There is also no objective evidence regarding the advantages of VATS lung resections over open surgery.

Postoperative care

1. Perioperative antibiotics
2. Optimal pain control
3. Early mobilization
4. Chest physiotherapy
5. Incentive spirometry
6. IPPB

Adjuvant therapy

- There is definite benefit with cisplatin-based adjuvant chemotherapy in completely resected NSCLC. Several recent large multicenter randomized controlled trials and a meta analysis showed a significant survival advantage with cisplatin-based postoperative chemotherapy in completely resected NSCLC. (Level Ia, Grade A)
- There is no role of adjuvant radiotherapy in completely resected early stage NSCLC. The PORT meta analysis showed higher mortality in patients treated with post operative radiotherapy compared to patients treated with surgery alone (Level Ia, Grade A)
- Adjuvant radiotherapy may be considered in patients with residual disease after lung resection or positive margins. (Level III, Grade B)

II. Patients with positive mediastinal lymph nodes (T1-3, N2)

Workup includes

1. Chest X-ray
2. CT scan chest and upper abdomen
3. Fiber optic bronchoscopy
4. Cyto/histological diagnosis – sputum cytology, bronchoalveolar lavage/brushings cytology, post bronchoscopy sputum cytology, CT guided FNAC
5. Mediastinoscopy and biopsy
6. Metastatic workup – MRI scan brain, PET-CT scan.

A. Preoperatively diagnosed N2 disease

- Patients with clinico radiological N2 disease should undergo mediastinoscopy for histological evidence of N2 disease. (Level Ib, Grade A)
- Patients should undergo multimodality treatment protocols.
- Patients are primarily treated with neoadjuvant chemotherapy followed by surgery. Four randomized trials have shown significantly improved survival with neoadjuvant chemotherapy compared to patients treated with surgery alone. (Level Ib, Grade A)
- Patients progressing on neoadjuvant chemotherapy should be treated with definitive chemoradiotherapy. (Level III, Grade B)
- Patients who do not progress on NACT and who have resectable disease should be treated with surgery provided they have adequate pulmonary reserve. (Level III, Grade B)
- Patients with inadequate pulmonary reserve to tolerate lung resection should be treated with definitive chemoradiotherapy. (Level III, Grade B)

B. Surgically discovered N2 disease

- Patients with N2 disease detected on thoracotomy should undergo lung resection provided the tumor can be completely resected. (Level III, Grade B)
- Systematic lymph node dissection should be done. (Level III, Grade B)
- Adjuvant therapy should be considered. (Level III, Grade B)

Adjuvant therapy

- The role of adjuvant radiotherapy in completely resected N2 NSCLC is unclear. Subset analysis in the PORT meta analysis showed no difference in survival
- Adjuvant radiotherapy may be indicated in patients with residual disease after surgery or positive margins. (Level III, Grade B)

III. Patients with locoregionally advanced disease (T4 and N3)

- Treatment of patients with T4 and N3 NSCLC is predominantly non surgical. (Level III, Grade B)
- **Patients with good performance status should be treated with combination chemo radiotherapy.** Evidence from a meta analysis and 12 randomized controlled trials show a survival benefit with cisplatin-based chemotherapy and radical radiotherapy compared to radiotherapy alone. (Level Ia, Grade A)
- Concurrent chemo radiotherapy is preferable to sequential chemo radiotherapy. (Level III, Grade B)
- There is no difference between daily and weekly chemoradiotherapy regimens. (Level Ia, Grade A)

- **Cisplatin based chemotherapy regimens are better than non-cisplatin based chemotherapy.** (Level Ia, Grade A)
- Patients who may not tolerate combination chemo radiotherapy should be treated with radiotherapy alone. (Level III, Grade B)
- Patients with malignant pleural effusion should be treated with pleurodesis. Palliative chemotherapy should be given in patients with good performance status. (Level III, Grade B)
- Highly selected patients with stage III B disease may benefit from surgery as part of multimodality treatment protocols. (Level IV, Grade C)

IV. Patients with metastatic disease

- The aim of treatment is palliation and prolongation of survival.(Level Ia, Grade A))
- **Patients with good performance score (ECOG 0, 1) should be treated with platinum-based combination chemotherapy.**(Level Ia, Grade A)
- Combination chemotherapy regimens are better than single agent chemotherapy (Level Ia, Grade A)
- Cisplatin-combinations have a higher response rate and may improve overall survival when combined with a third-generation agent, but have higher toxicities. The second agent should be a third generation chemotherapy agent like docetaxel, paclitaxel, gemcitabine, pemetrexed, vinorelbine and irinotecan. (Level Ia, Grade A))
- Patients with tumours that have EGFR-activating mutations should be treated with an oral tyrosine kinase inhibitor. If EGFR mutation status is negative or unknown, then cytotoxic chemotherapy should be used. (Level I, Grade A))
- In patients with non-squamous histology, Pemetrexed based combination chemotherapy can be considered (Level Ib, Grade A)).
- Bevacizumab can be added to carboplatin-paclitaxel chemotherapy in the first-line setting, except in patients with squamous histology, brain metastases, clinically significant hemoptysis, inadequate organ function, PS > 1, therapeutic anticoagulation, uncontrolled hypertension or clinically significant cardiovascular disease. Bevacizumab can be continued until progression of disease. (Level Ib, Grade A))
- Bevacizumab can be dosed at 7.5 mg/kg or 15 mg/kg IV every 3 weeks.(Level Ib, Grade A))
- Cetuximab can be added to cisplatin-vinorelbine chemotherapy in the first-line setting, in patients with EGFR-positive tumour as measured by IHC. Cetuximab can be continued until progression of disease. (Level I, Grade A))
- Elderly patients (> 70 years) or patients with ECOG performance status 2 can be considered for chemotherapy, either single agent or in selected patients, combination chemotherapy. These patients benefit from chemotherapy, although the degree of benefit is less than for PS 0 and 1 patients and toxic effects of chemotherapy are more.
- Patients with poor performance score (ECOG 3 and 4) should be treated with best supportive care (BSC). (Level Ia, Grade A)

- In patients receiving first-line chemotherapy, 4 to 6 cycles of chemotherapy should be administered.(Level I, Grade A))
- Maintenance chemotherapy with either docetaxel, pemetrexed or oral tyrosine kinase inhibitor may prolong progression-free survival and can be considered after completing first-line chemotherapy.(Level I, Grade A))
- Painful bone metastases and metastases in weight-bearing bones should be treated with palliative radiotherapy.(Level Ia, Grade A)
- Bisphosphonates may reduce adverse bone events in patients with bone metastases. (Level Ia, Grade A)
- Highly selected patients with solitary brain, adrenal and lung metastasis may benefit from resection of the metastasis along with lung resection. (Level IV, Grade C)
- In patients who have progressed after first-line therapy, and who have adequate performance status, second line therapy may be considered including pemetrexed, docetaxel, erlotinib or gefitinib.(Level I, Grade A))
- Second-line therapy can be continued as tolerated until disease progression.
- Patients who have progressed on second-line therapy may be considered for erlotinib therapy, if they have not received a prior oral tyrosine kinase inhibitor.(Level I, Grade A))

Management of malignant pleural effusion (unknown primary)

Workup includes

1. Clinical examination – look for primary in breast, lungs, abdomen, pelvis; lymph node biopsy if enlarged (lymphoma)
2. Chest X-ray
3. Pleural fluid cytology
4. Tumor markers – CEA, CA-125 (females) and CEA, PSA (males)
5. Fiber optic bronchoscopy
6. Thoracoscopy – if pleural fluid cytology is negative

- The best palliation for patients with malignant pleural effusion with complete lung expansion after chest tube drainage is pleurodesis.
- Talc has better results in pleurodesis than bleomycin and tetracycline.
- Patients with incomplete lung expansion after chest tube drainage may be treated with a pleuro peritoneal shunt or an indwelling pigtail catheter.
- Palliative chemotherapy may be offered to patients with good performance status

Radiotherapy Protocols

Radical Radiotherapy

Indications – in early NSCLC – medically unfit for surgery or patient refusing surgery.

60-65 Gy / 33-36 fr / 6-7 weeks

Phase I : 40 Gy / 20 fr across the mediastinum

Phase II : 10 Gy / 6 fr / 2 cm margin (spinal cord shielding)

Phase III : 10-15 Gy / 1 cm margin

Supraclavicular fossa is included as primary coverage in upper lobe tumors.

Palliative Radiotherapy

Indications – unresectable disease

KPS > 60%

39Gy / 13 fr / 2.5 weeks

Phase I : 30Gy / 10 fr / 2 weeks / maximum margin 2 cm

Phase II : 9Gy / 3 fr / 3 days / spinal cord shielding

KPS = 60%

10Gy / 1 fr / 1 day (or) 17Gy / 2 fr / 1 week (or) 20Gy / 5 fr / 1 week

(No difference in IAEA pilot study)

Supra clavicular fossa is not included in the field.

Postoperative Radiotherapy

Indications – Positive margins and residual disease

50-54Gy / 25-27 fr / 5-6 weeks

Phase I : 40Gy / 20 fr across the mediastinum

Phase II : 10-14Gy / 5-7 fr / 2 cm margin (spinal cord shielding)

Metastatic Disease

Parenchymal Brain Metastases

30Gy / 10 fr / 2 weeks

Low performance score – 20Gy / 5 fr / 1 week

Spinal Cord Compression

30Gy / 10 fr / 2 weeks (or) 20Gy / 5 fr / 1 week

(along with steroids and supportive care)

Painful bone metastases

Single fr : 6-8Gy / 1 fr

Multiple fr : 30Gy / 10 fr / 2 weeks (or) 20Gy / 5 fr / 1 week

Rarely, hemibody irradiation may be used for multiple bone metastases

Endobronchial Radiotherapy

Indications – salvage treatment for recurrent / residual endobronchial lesion.

7.5Gy / fr X 2 fr 1.2 weeks apart 1 cm off axis.

Superior Vena Cava Syndrome

20Gy / 5 fr / 1 week – assess the response

20Gy / 10 fr / 2 weeks with reduced fields

(along with steroids and supportive care)

Small Cell Lung Cancer

Small cell lung cancer (SCLC) represents a distinct entity that is biologically and clinically different from Non Small cell Lung cancer. It is an aggressive cancer with a rapid proliferation index thereby making it very chemosensitive.

SCLC is staged according to the International Association for Study of Lung Cancer, into Limited stage disease (LD) and Extensive stage disease (ED).

Limited stage disease (LD) is defined as disease restricted to one hemithorax, with or without involvement of ipsilateral regional nodes including hilar, mediastinal and supraclavicular. It also includes involvement of contralateral mediastinal and supraclavicular nodes and an ipsilateral pleural effusion.

Disease more extensive than described above is considered Extensive stage disease (ED).

Management of LD SCLC

Patients with LD SCLC are treated for potential cure with chemoradiotherapy. The standard treatment of LD SCLC is concurrent radiation therapy with cisplatin based chemotherapy. (Level IIa, Grade B)

Role of chemotherapy

SCLC are known to be chemosensitive tumours and have shown good response rates with cisplatin based chemotherapy. Current standard chemotherapeutic protocol is to give 4-6 cycles of cisplatin and etoposide based regimen. (Level IIa)

However, even with this protocol- though response rates were as high as 70-80% (including 50% complete responses), most patients still die of tumour progression/recurrence.

Therefore, newer chemotherapeutic regimens with dose intensification were attempted. These showed very high toxicities with no documented significant increase in survival in all phase II-III studies. (Level Ib, Grade A)

Role of Radiation therapy (RT) in LD SCLC

In patients treated with chemotherapy alone, locoregional failure in the thorax occurs in upto 80% of patients with SCLC.

RT was accepted as a part of combined modality approach as a result of 2 meta-analyses which clearly showed an improvement in local control with subsequent improvement in overall survival (Level Ia, Grade A). Thoracic RT should be administered early, i.e during the 1st or 2nd cycle of chemotherapy at curative doses to achieve increase in the overall survival. (Level Ib, Grade A)

Role of Surgery

Surgery plays a much less definitive role in SCLC as compared to NSCLC.

The available data indicate that surgery can be useful in T1, T2 tumours without nodal involvement. For small lesions, surgery can also be considered as first line treatment followed by chemotherapy.

(Level IV, Grade C)

Role of Prophylactic Cranial Irradiation (PCI)

The central nervous system is a frequent site for metastases in SCLC (about 50% of isolated metastases) which results in significant morbidity.

In a meta-analysis performed by the Collaborative Group, PCI showed an absolute increase of 5.4% in 3 year survivals with an increase of 8.8% in the disease free survival. (Level Ia, Grade A) However the role of PCI, regarding the timing, dose and fractionation, eligibility of patients and neurological toxicity remains unclear.

In conclusion, the standard accepted treatment for LD SCLC of the lung is concurrent chemoradiation (platinum based) with emphasis on an early start of thoracic radiation. Surgery has a small role to play in small peripherally located tumours.

Management of Extensive stage SCLC

Platinum based chemotherapy remains the mainstay of management of ED SCLC.

Two meta-analyses have clearly indicated the superior role of cisplatin based chemotherapy regimens as compared to other agents.

(Level Ia, Grade A)

Carboplatin can also be used as an alternative to cisplatin, with no difference in efficacy or toxicity. The usual course of management is to give 4 cycles of cisplatin/carboplatin with etoposide. There is no evidence for the use of maintenance therapy in ED SCLC outside of a trial setting. (Level Ib, Grade A) Further, there is no evidence for the use of dose intensification or change of chemotherapeutic agent. Trials have shown no increase in survivals with the above measures.

Management of refractory/relapsed ED SCLC

In spite of being very chemosensitive, the progression free survival in ED SCLC, after chemotherapy, is only 4 months. Most patients will relapse and the prognosis of such patients is very poor.

For patients relapsing after 3 months from completion of induction treatment the same protocol as induction can be repeated. For patients who relapse within 3 months of induction, or for refractory disease, 2nd line chemotherapy should be given. (Level IV, Grade C) Topotecan used as a single agent is at present the best option available.

(Level Ib, Grade A)

Surgery plays no role in management of ED SCLC.

In all cases of ED SCLC supportive care should include, radiation therapy for bony metastases and the management of paraneoplastic syndromes.

In conclusion, as ED SCLC is a disease with a poor prognosis to begin with and complete treatment will increase survival only by 8-10 months, good patient selection is of utmost importance. Age and performance status form important patient selection criteria. In fit patients, chemotherapy is the standard of care.

PEDIATRIC SOLID TUMORS

XV. WHEN TO SUSPECT/ RECOGNIZE?

d) Introduction:

Pediatric solid tumours are a very diverse group of diseases with differing biologies and behaviours and a substantial proportion consists of characteristic entities that are rarely seen in adults.

e) Case definition:

The International Classification of Childhood Cancer, Third Edition (ICCC-3) contains 12 main diagnostic groups:

- I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases
- II. Lymphomas and reticuloendothelial neoplasms
- III. CNS and miscellaneous intracranial and intraspinal neoplasms
- IV. Neuroblastoma and other peripheral nervous cell tumors
- V. Retinoblastoma
- VI. Renal tumors
- VII. Hepatic tumors
- VIII. Malignant bone tumors
- IX. Soft tissue and other extraosseous sarcomas
- X. Germ cell tumors, trophoblastic tumors and neoplasms of gonads
- XI. Other malignant epithelial neoplasms and malignant melanomas
- XII. Other and unspecified malignant neoplasms

All of the groups except retinoblastoma are split into subgroups, and the most heterogeneous subgroups are in turn split into divisions.

The pediatric solid tumors comprise of group III to XII. Group III and VIII requiring specialized orthopedic and neuro-surgery and neuro-radiation expertise are considered separately.

XVI. INCIDENCE OF THE CONDITION IN OUR COUNTRY

The annual incidence of cancer in children under 15 years of age is between 38 and 124 per million. There is no organized Paediatric solid tumours registry in India; hence, robust epidemiologic data is not available for the country. All currently quoted data is based on population-based cancer registries across India under the National Cancer Registry Program.

XVII. DIFFERENTIAL DIAGNOSIS

- Trauma
- Infection
- Benign tumor

XVIII. PREVENTION AND COUNSELING

The occurrence and progression of paediatric solid tumours like most other tumors is influenced by a variety of genetic changes. The accumulation of changes varies between tumor types and the exact pattern varies even for a particular tumor type. Genetic counseling is the communication of information and advice about inherited conditions. A standard medical history and examination is required for the affected person and in addition the family pedigree needs to be constructed. For certain tumor syndromes it might also be necessary to examine apparently normal parents and other relatives for minor features of the condition. Alternatively, if a specific mutation is identified in the proband, genetic testing for this mutation can subsequently be offered to the relatives where appropriate. Counseling needs to include all aspects of the condition and the depth of explanation should be matched to the educational background of the couple. Parents may feel responsible for the condition of their child. These fears need to be aired and allayed. In inherited tumors and syndromes there is an additional need to minimize feelings of guilt and stigmatization.

XIX. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

*Situation 1: At Secondary Hospital/ Non-Metro situation: Optimal Standards of Treatment in Situations where technology and resources are limited

g) Clinical Diagnosis:

History & Clinical Examination

Documentation of congenital anomalies, evident signs of clinical syndromes

Assessment of Performance Status and Nutrition

h) Investigations:

i. **Baseline investigations**

Complete Haemogram	Hemoglobin, RBC, WBC, Platelets, ESR, Coagulation Profile
Routine Biochemistry	FBS, RFT, LFT & LDH
Serology	HbsAg, HCV, HIV

ii. **Histological Examination:** (Immunohistochemistry)

Tissue diagnosis	FNAC, Biopsies, Cytology, bone marrow studies
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iii. **Diagnostic Imaging:** Contemporary imaging modalities

Radiology	X-ray, USG, CT scan
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i) Treatment:

Standard Operating procedure

b. In Patient

- All sick pediatric solid tumor patients are admitted for supportive care and initiation of treatment as required.
- Patients planned for elective surgery are admitted a day prior to the surgery with complete work-up and treatment plan.
- Patients with fever are admitted for management of Febrile Neutropenia. Once their condition is stable they are discharged and followed up in the OPD.

a. Out Patient

- Patients undergo complete clinical evaluation and are recommended investigations to confirm the diagnosis and complete staging.
- Sick patients and those with Medical oncologic emergencies are admitted in the ward for emergency management.
- Stable patients are followed up in the OPD till the diagnosis and staging workup is complete.
- Treatment decisions are taken in the Multidisciplinary Joint clinics at diagnosis, at the time of local therapy planning, at time of completion of treatment and if required anytime in between.

b. Day Care

- Treatment for all stable pediatric solid tumor patients is started in the OPD/Day care. Admission is limited to patients with uncontrolled co-morbid conditions or complications of the disease or treatment related complications. .
- Patients with advanced/relapsed disease not amenable to treatment are considered for palliative care and referred for the same.

j) Referral criteria:

- Patients requiring additional investigations or expert opinion to be referred to institutions with adequate infrastructure and expertise.

***Situation 2: At Super Specialty Facility in Metro location where higher-end technology is available**

k) Clinical Diagnosis:

History & Clinical Examination

Documentation of congenital anomalies, evident signs of clinical syndromes

Assessment of Performance Status and Nutrition

l) Investigations:

i. Baseline investigations

Complete Haemogram	Hemoglobin, RBC, WBC, Platelets, ESR, Coagulation Profile
Routine Biochemistry	FBS, RFT, LFT & LDH
Serology	HbsAg, HCV, HIV

ii. Histological Examination: (Immunohistochemistry)

Tissue diagnosis	FNAC, Biopsies, Cytology, bone marrow studies
Molecular pathology	EWS-FLI 1, EWS-WT1, SYT-SSX1, n-myc, PAX-3FKHR etc
Tumor Markers	AFP, BHCG, Urinary VMA, HVA

iii. Diagnostic Imaging: Contemporary imaging modalities

Radiology	X-ray, USG, CT scan, MRI
Nuclear imaging	PET scan, Bone scan, MIBG scan

m) Treatment:

Standard Operating procedure

c. In Patient

- All sick pediatric solid tumor patients are admitted for supportive care and initiation of treatment as required.
- Patients planned for elective surgery are admitted a day prior to the surgery with complete work-up and treatment plan.
- Patients with fever are admitted for management of Febrile Neutropenia. Once their condition is stable they are discharged and followed up in the OPD.

a. Out Patient

- Patients undergo complete clinical evaluation and are recommended investigations to confirm the diagnosis and complete staging.
- Sick patients and those with Medical oncologic emergencies are admitted in the ward for emergency management.
- Stable patients are followed up in the OPD till the diagnosis and staging workup is complete.
- Treatment decisions are taken in the Multidisciplinary Joint clinics at diagnosis, at the time of local therapy planning, at time of completion of treatment and if required anytime in between.

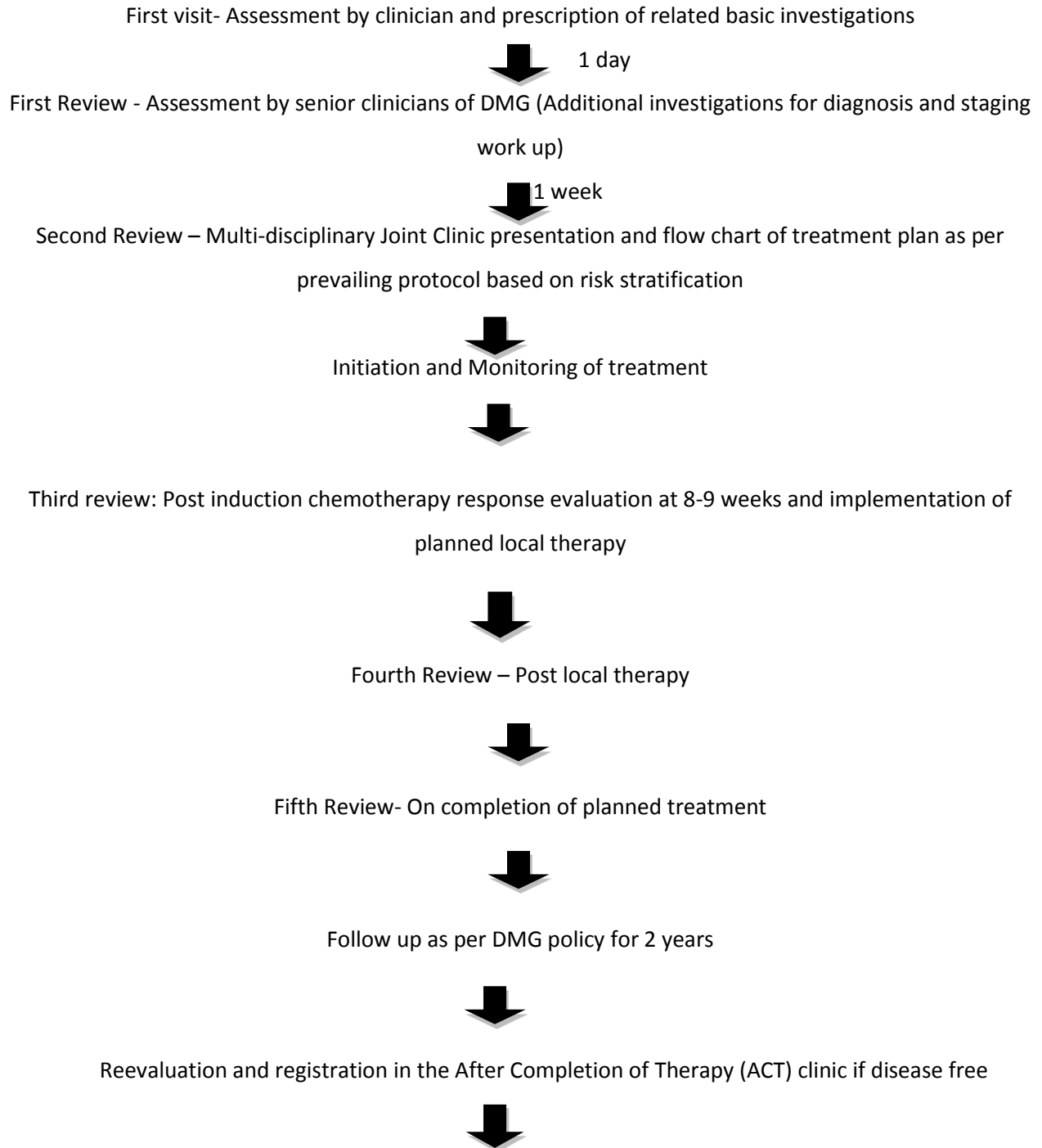
b. Day Care

- Treatment for all stable pediatric solid tumor patients is started in the OPD/Day care. Admission is limited to patients with uncontrolled co-morbid conditions or complications of the disease or treatment related complications. .
- Patients with advanced/relapsed disease not amenable to treatment are considered for palliative care and referred for the same.

n) Referral criteria:

- Patients with logistic problems will receive referral letters for institutions with adequate infrastructure and expertise including the necessary protocols.
- Patients with advanced incurable disease will be triaged and will undergo counseling by the DMG's palliative care team. Appropriate instruction and arrangement will be provided for referral of these patients for supportive care to institutions at convenient distance from their hometowns.

XX. WHO DOES WHAT? and TIMELINES



Follow up in ACT clinic annually to monitor growth and development, late effects and encourage survivorship programme – “UGAM”

XXI. FURTHER READING / REFERENCES

- Steliarova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. Cancer 2005;103:1457–1467
- Arora RS et al. Epidemiology of Childhood cancer in India. Indian J Cancer 2009;46:264-273
- Hodgson SV, Maher ER, Eng C, Foulkes W. A practical guide to human cancer genetics. Cambridge University Press, Cambridge (2006).

RESOURCES REQUIRED FOR ONE PATIENT / PROCEDURE (PATIENT WEIGHT 60 KGS)

(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

HUMAN RESOURCES	INVESTIGATIONS	DRUGS	EQUIPMENT
1. Qualified Surgeon 2. Qualified Radiation Oncologist 3. Qualified Pediatric Medical Oncologist 4. Pathologist 5. Radiologist 6. Trained Nurses 7. General Physician 8. Palliative Care specialist 9. Anesthetist 10. Clinical Psychologist 11. Medical Social Worker	Haematological, Biopsy, Histopathology, CT Scan/MRI, Molecular (IHC) analysis.	NSAIDs, Opioids Antacids, Antiemetics, Contrast medium Chemotherapeutics (Most commonly used drugs) Vincristine, Ifosphamide, Doxorubicin, Cisplatin, Carboplatin, Etoposide, Cyclophosphamide, Actinomycin D, Bleomycin, Topotecan, Methotrexate, Temozolamide, 13 cis-Retinoic acid,	OT equipment, Electrical cautery, Hormonic scalpel, Intaoperative X-ray unit, Anesthesia trolley, mechanical ventilators, Suction apparatus, nebulizers, Co60 unit, Linear Accelerator, 2D/3D Simulators, Treatment planning system,

Neuroblastoma

Neuroblastoma is the most common extra cranial solid tumor in children. It arises from neural crest cells which differentiate in cells of the sympathetic ganglia and adrenal medulla.

It remains a complex medical challenge with spontaneous regression at one end to an unpredictable clinical course and dismal outcome at the other end of spectrum.

Image defined risk factors (IDRF) for Neuroblastoma

Site of primary tumor: Cervical, cervico-thoracic, thoracic, thoraco-abdominal, abdominal, and pelvic.

Local extent:

- Crossing midline
- Encasement of any major vessel at that site like carotid, vertebral, IJV, subclavian, mediastinal great vessels, abdominal aorta and its branches, IVC, iliacs.
- Infiltration of adjacent critical areas like skull base, trachea, main bronchi, brachial plexus, pericardium, , costo-vertebral junction (especially between D9-D12), porta-hepatis, hepato-duodenal ligament, mesenteric root, sciatic notch, intra-spinal extension (more than 1/3rd diameter of spinal canal involved on axial image or loss of perimedullary space or abnormal cord)
- Infiltration of adjacent organs like heart, diaphragm, liver, kidney, spleen, pancreas, etc

Presence of multifocal primary

Collections in cavities like pleural or peritoneal

Adenopathy: Enlarged local or distant nodes

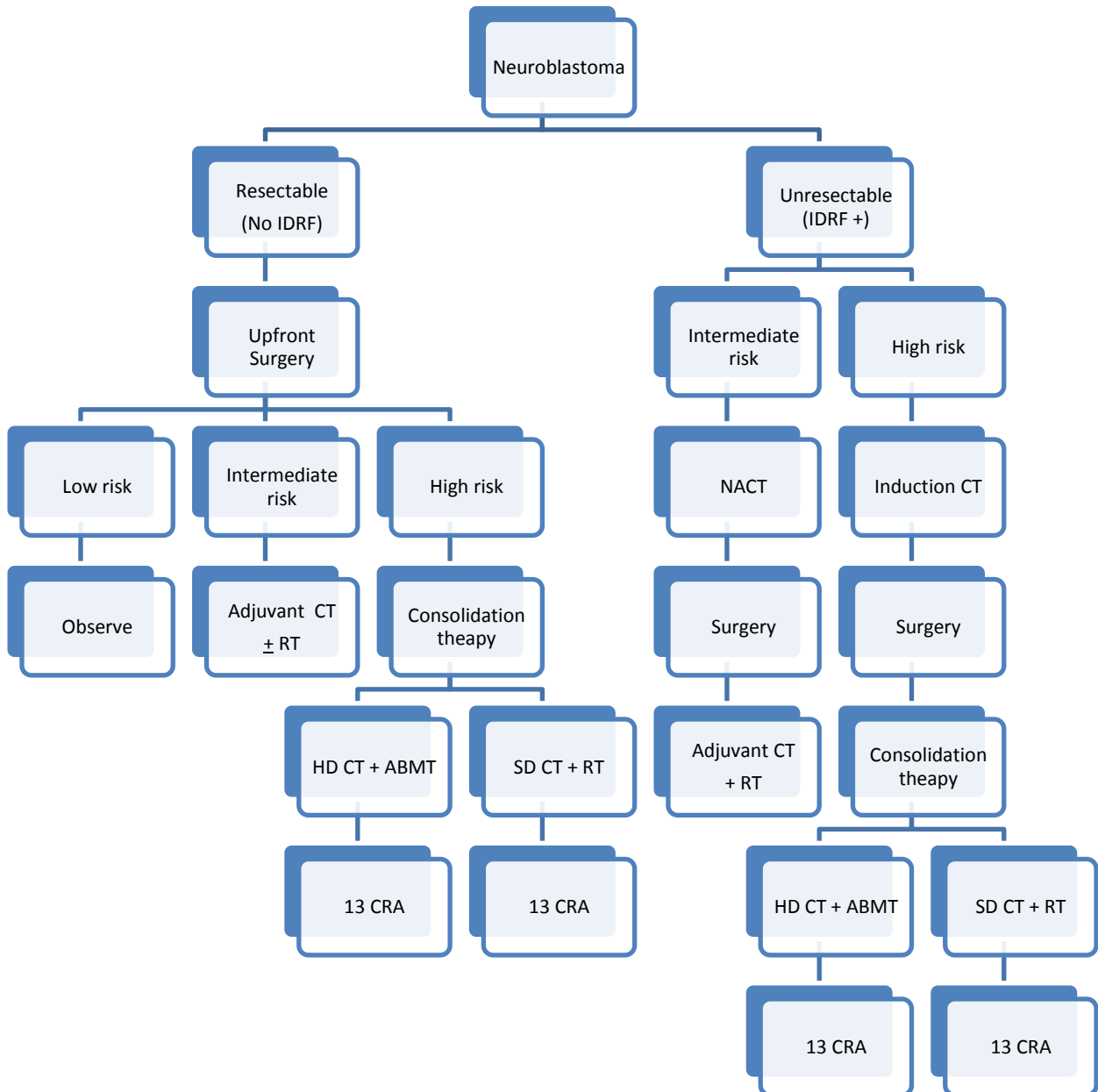
Metastatic disease: Bony lesions, Liver or lung lesions

Neuroblastoma risk Stratification

- Risk stratification should be done at a tertiary centre before initiation of therapy.
- In unresectable lesions generous core biopsy (image guided) should be performed for histopathology and molecular studies.

Risk	Age	Stage	MYCN status
Low	<547 days	1, 2A/B,4S	NA
	≥ 547 days	1, 2A/B	NA
Intermediate	<547 days	3, 4	NA
	≥ 547 days	3	NA
High	<547 days	1, 2, 3, 4, 4S	Amp
	≥ 547 days	1,2,3	Amp
	≥ 547 days	4	Any

Management Algorithm



HD CT = High Dose Chemotherapy
SD CT = Standard Dose Chemotherapy
ABMT = Autologous Bone Marrow Transplant
13 CRA = 13 Cis Retinoic Acid

Wilms' tumor

Wilms' tumor predominantly affects children under 5 years of age, most commonly during the first 2 years of life. Contemporary treatment of Wilms' tumor has led to an overall survival of over 85% and the emphasis is now shifting from successful treatment to reducing treatment-associated morbidity without loss of efficacy.

Radiological report for Wilm's Tumor

Should be a contrast enhanced CT/MRI of abdomen

Laterality: Right or Left or Bilateral disease

Location: which pole

Size

Local extent:

- Is it Completely Intra-renal location or is Perinephric spread evident
- Renal sinus infiltration.
- Renal vein status
- IVC status.
- Renal artery : comment about the abdominal origin as well, comment on accessory arteries if any
- Infiltration of liver, pancreas, bowel, GB, or abdominal wall

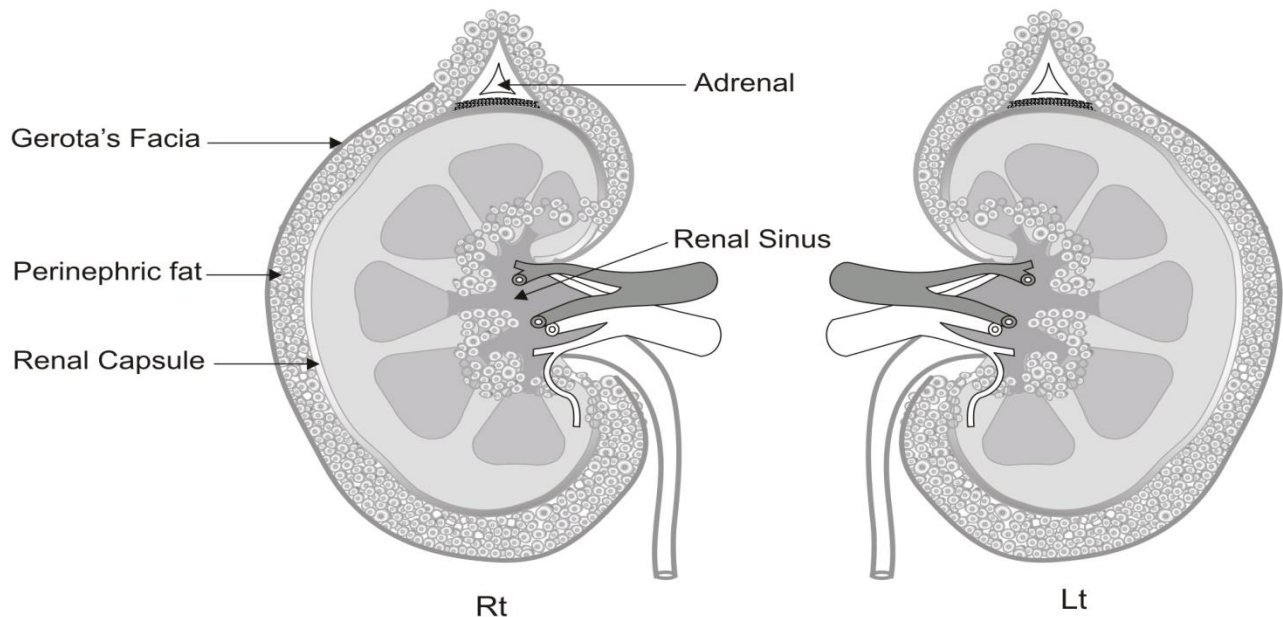
Significant ascites, Peritoneal implants

Adenopathy: Enlarged nodes

Metastatic disease: Lung, liver, bone or extra-abdominal nodes

Synoptic Pathology report for renal tumour

Gross Examination: Received a specimen of right / left radical nephrectomy / nephrectomy/ partial nephrectomy measuring -----X-----X----- cm. including perinephric fat. Hilum of the kidney shows ureter measuring -----cm along with arterial and venous stumps. On cutting open, the kidney measures -----X-----X-----cm and shows a tumour measuring -----X-----X----- cm involving-----of the kidney. Cut surface of the tumour is solid / nodular solid / solid-cystic. Areas of necrosis and hemorrhage are----- . Tumour invades through the renal capsule and extends into perinephric fat grossly / does not invade the renal capsule. Tumour involves / does not involve the Gerotta's (renal)fascia. Renal sinus is----- . Renal vein invasion is----- . Renal pelvis and ureter are----- . Resection end of ureter is ----- Resection end of renal vein is ----- . Hilum of the kidney reveals-----nodes. Foci of nephroblastomatosis are not indentified / identified . A slice of the tumour is cut in a grid fashion and submitted for histopathology examination.



Please draw the tumour and indicate tumour grid in the above diagram

Block identification:

- I-
- II-
- III-
- IV-
- V-

Microscopy:

Right / Left radical nephrectomy / Nephrectomy / Partial nephrectomy ,
 Post chemotherapy / History of neo-adjuvant chemotherapy unknown-

Triphasic / Biphasic / blastemal predominant / teratoid Wilm’s tumour of -----kidney.

Favourable histology (FH) / unfavourable histology (UH)

Anaplasia is absent. Focal / diffuse anaplasia is seen.

Vascular invasion -----

Tumour does not invade the renal capsule / invades the renal capsule and is seen in perinephric fat..

Gerotta’s fascia is -----

Renal sinus involvement is-----

Renal vein involvement is -----

Hilar lymph nodes-----

Foci of nephroblastomatosis are not seen / -----type of nephroblastomatosis is present. -----

Resection margins of ureter, renal vein and renal artery are -----

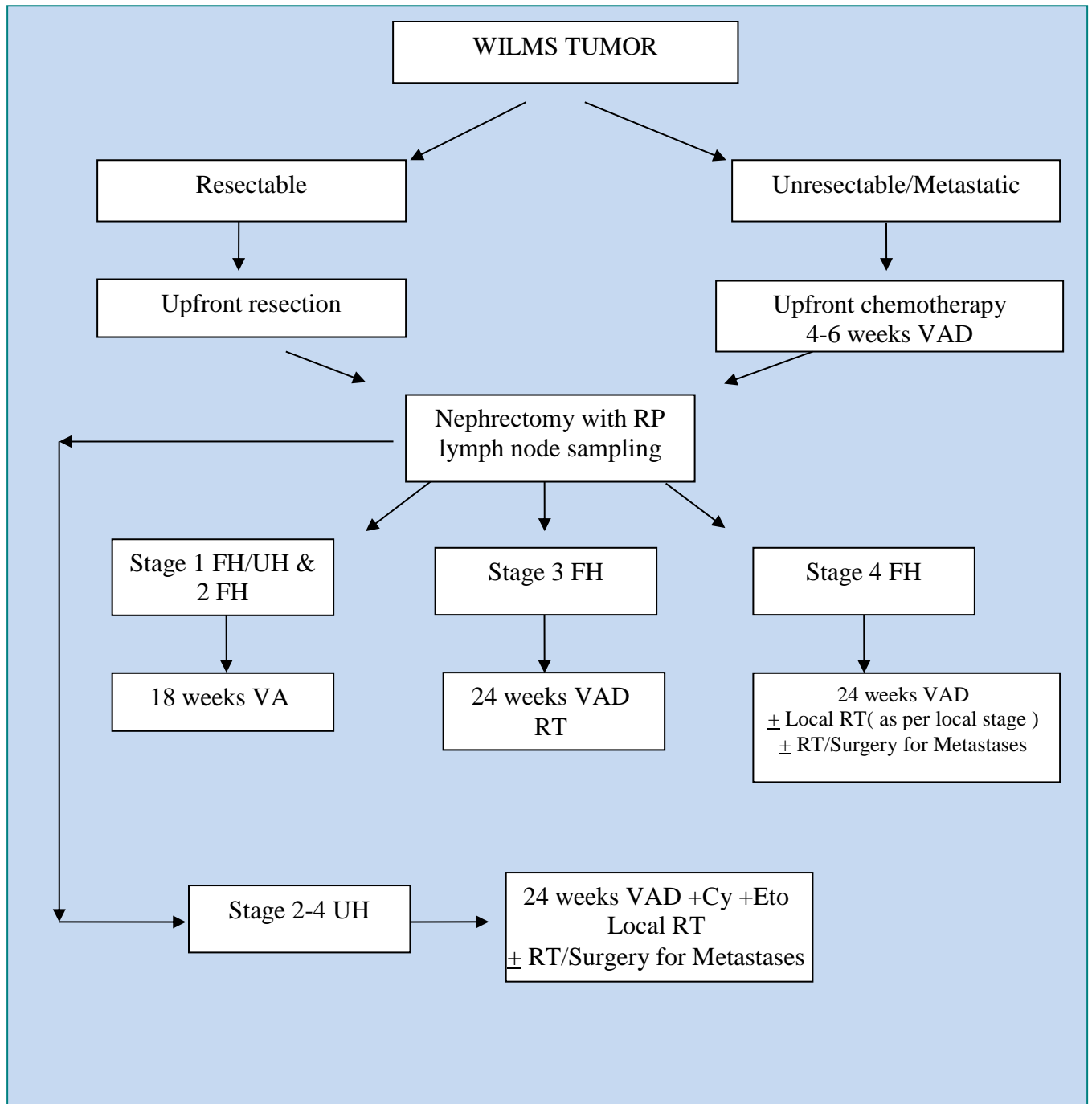
Adrenal is -----

Impression:

Right / Left radical nephrectomy / Nephrectomy / Partial nephrectomy ,
 Post chemotherapy / History of neo-adjuvant chemotherapy unknown.:

Wilm’s tumour, -----histology, -----invading renal capsule / -----
 invading Gerotta’s fascia, -- -----involving -----lymph nodes.

Management Algorithm



V= Vincristin A= Actinomycin D D= Doxorubicin
 Cy = Cyclophosphamide Eto= Etoposide
 RP = Retroperitoneal RT= Radiotherapy
 FH=Favourable Histology UH= Unfavourable Histology