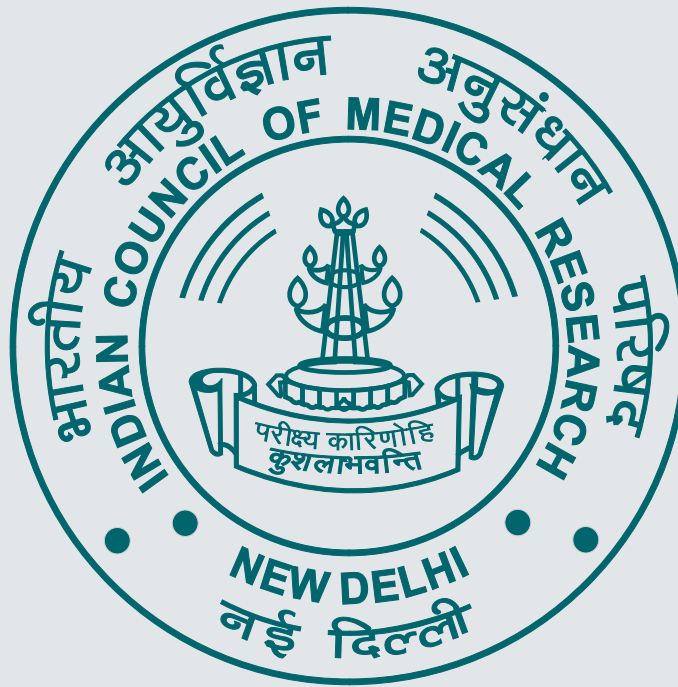# INDIAN COUNCIL OF MEDICAL RESEARCH

# CONSENSUS DOCUMENT FOR THE MANAGEMENT OF CANCER CERVIX

*Prepared as an outcome of ICMR Subcommittee on Cervix Cancer*

**Indian Council of Medical Research**
**2016**

# CONSENSUS DOCUMENT FOR THE MANAGEMENT OF CANCER CERVIX

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# Foreword

I am glad to write this foreword for consensus document for management of cancer cervix. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This consensus document on management of cervix cancer summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in formulating site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. Hope that this document would provide guidance to practicing doctors and researchers for the management of patients suffering from cervix cancer and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of Consensus Document on Management of Cancer Cervix would serve the desired purpose.

(Dr.Soumya Swaminathan)
Secretary, Department of Health Research
and Director-General, ICMR

# Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.

The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

# Preface

The cancer of uterine cervix is the commonest cancer among the women in India. However, the incidence is gradually reducing especially in urban areas as observed in the population based registries. The treatment of early stage cancer cervix is either radical surgery or radical radiotherapy with similar results, whereas, for advanced stages the treatment remains as chemo-radiation. There has been several advances and refinement in the treatment modalities for treatment of cancer cervix in past few years.

The management of carcinoma cervix should be well defined and accomplished. It has been noticed that there are variations in the treatment pattern across the country. It is an admirable initiative of the ICMR for setting-up task force to bring out the consensus document for the management of cancer cervix. These guidelines will be useful to the practicing clinicians and students to optimize the treatment of their patients. This will also bring the uniformity in the management across the country and establish collaborative studies. This will also help in bringing out Indian data related to outcome and toxicity of the treatment and further refinement of management and research in this area.

I am grateful to all members of the task group, who have been expert in their field, for devoting their valuable time from their busy schedule and remained committed to their assigned task. I would like to thank Dr GK Rath for his untiring support, inspiration and guidance and Dr Tanvir Kaur for her continuous efforts and support in all meetings.

The ICMR deserves special thanks for these consensus documents. The consensus on the management of cancers is a dynamic process in view of emerging evidence, and these will also be updated regularly as the evidence evolves with newer knowledge. We would be happy to receive constructive feedback to further improve this document for the benefit of our patients.

Shyam Kishore Shrivastava
Chairman
Sub-Committee for Carcinoma Cervix

# Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr. R.S. Dhaliwal)
Head, NCD Division

# Acknowledgement

The Consensus Document on Management of Cervix Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Soumya Swaminathan, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking her special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients.

I would like to thank Dr. RS Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged..

(Dr.Tanvir Kaur)
Program Officer & Coordinator

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# 1 INTRODUCTION

Cervical cancer remains a significant cause of morbidity and mortality among women globally, even though it is the cancer with the greatest potential for secondary prevention. In some regions of the world the incidence is alarmingly high, which includes India[1, 2], however in some regions in India there is decline in AARs over past few years[3]. This disease is highly preventable and curable. A number of guideline documents are available for the management of common cancers in the published literature. Large academic institutions typically produce their own local guidelines and use them on a daily basis. In this document, all the recommended interventions are based on scientific evidence with the level of evidence and/or grade of recommendation indicated.

## 1.1 EPIDEMIOLOGY

Cervical cancer is most common cancer in Indian women though breast is the leading cancer site globally. In India, cervical cancer had increased from 0.11 million in 2000 to 0.16 million in 2010[4]. The proportion ranged from 15% to 55% of female cancers from different parts of the country. Over 80% of the cervical cancer present at a fairly advanced stage and annually around 80,000 deaths are reported in India[5]. According to global cancer statistics, cervical cancer is now the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008. More than 85% of these cases occur in developing countries. India, the second most populous country in the world, accounts for 27% (77,100) of the total cervical cancer deaths[6]. The disproportionately high burden of cervical cancer in developing countries and elsewhere in medically underserved populations is largely due to a lack of screening that allows detection of precancerous and early stage cervical cancer[6,7].

It is now well recognized that cervical carcinogenesis occur in a stepwise fashion. This transition of normal epithelium to pre-neoplastic lesions and invasive carcinoma occur sequentially and progress through well recognized stages and takes approximately 10–20 years to develop an overt malignancy. The natural history of the disease suggests that screening should initially target those women who have higher prevalence of high grade precancerous lesions (CIN2/CIN3) – women mostly in their 30s and 40s. In India, the incidence of cervical cancer significantly rises around the age of 45 years and peaks at 55 years of age. Persistent infection of Human Papilloma Virus (HPV), a sexually transmitted double-stranded DNA virus is considered the most significant and 'necessary' casual agent for the development of cancer of uterine cervix. To date, more than 140 human and animal papilloma virus genotypes have been characterized and sequenced. Approximately 30 HPVs that infect the ano–genital tract, of these 15 HPV types classified as 'high-risk' types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are associated with high grade cervical cancer precursor lesions and invasive cervical cancers. Molecular and clinico-epidemiological studies have demonstrated that HPV types 16 and 18 are

the two most common oncogenic HPV types found in invasive cervical cancer and high-grade cervical intraepithelial neoplastic (CIN) lesions. On the other hand, 11 different HPV types classified as 'low-risk' types (HPV types 6, 11, 40, 42, 43, 44, 54, 61, 70, 81 and CP6108) are mainly associated with genital warts and benign cervical lesions. Among these, HPV6 and HPV11 cause approximately 90% of genital warts. In addition to HPV infection, co-factors such as parity, early age of marriage, genital hygiene, promiscuity, use of oral contraceptives, smoking, immune suppression (eg HIV), infection with other sexually transmitted agents and poor nutrition have been associated with the development of cervical cancer[8,9].

In India, the prevalence of HPV in cervical intraepithelial lesion and cancer is > 80% and the high risk HPV 16/ 18 compiles in about > 90% of the cervical cancer cases. A population-based, cross-sectional survey in married women aged 16–59 years was conducted in rural Dindigul district, Tamil Nadu[10]. Recently, it has been shown that a single round of HPV screening can cause a significant reduction in the severity and mortality of the disease[11]. In India, approximately 90% of invasive cervical cancer cases are squamous cell carcinoma, while 10–12% is adenocarcinomas. In a national HPV mapping study in India, prevalence of HPV16 was found to be highest in Chennai (88%), and lowest in Jammu and Kashmir (14.2%)[12,13].

The most effective secondary preventive strategy for cervical cancer is systematic screening of women through an organized program along with treatment and follow-up of the screen detected precursor lesions. Cervical screening should be advocated for all ever sexually active women within a certain age group irrespective of whether they have any complaints, because there are often no signs and symptoms of cervical precancers. The national guideline for cervical cancer screening in India advocates screening of women between 30 years to 59 years of age. The focus on detection and prevention of cervical cancer must be emphasized in a highly populated country like India.

# 2 PRE-TREATMENT EVALUATION FOR CERVICAL CANCER

## 2. Pretreatment Evaluation

- Complete physical and gynecological examination (Examination Under Anesthesia if required to confirm the stage)

- Complete Blood Count and Biochemistry

- Cervical biopsy: punch biopsy / wedge biopsy/ conization with electrosurgical loops or knife-histopathological confirmation of malignancy is mandatory before starting the treatment

- Chest radiograph

- Optional investigations: The findings to be used to tailor the treatment rather than change the staging

    - Ultrasonography abdomen and pelvis

    - CT Scan

    - MRI

    - PET-CT Scan

    - Cystoscopy / Procto-Sigmoidoscopy / Barium enema / Intra Venous Urogram - if clinical suspicion of bladder, ureter or rectal involvement.

# 3 HISTOPATHOLOGIC TYPES

Modified World Health Organization histological Classification of Invasive carcinoma of the uterine cervix

### Squamous Cell Carcinoma

– Microinvasive (early invasive) squamous cell carcinoma

– Invasive squamous cell carcinoma

- Keratinizing

- Nonkeratinizing

- Basaloid

- Verrucous

- Warty

- Papillary

- Squamo-transitional

- Lymphoepithelioma-like carcinoma

### Adenocarcinoma

– Usual type adenocarcinoma

– Mucinous adenocarcinoma

- Endocervical type

- Intestinal type

- Signet-ring type

– Minimal Deviation

– Villoglandular

– Endometrioid adenocarcinoma

– Clear cell adenocarcinoma

– Serous adenocarcinoma

– Mesonephric adenocarcinoma

## Other Epithelial tumors

– Adenosquamous carcinoma

- Glassy cell variant
- Adenoid Cystic carcinoma
- Adenoid basal carcinoma
- Neuroendocrine tumors
- Carcinoid
- Atypical carcinoid
- Small cell carcinoma
- Large cell Neuroendocrine carcinoma

– Undifferentiated carcinoma

CHAPTER

*4* STAGING

FIGO Staging 2009
(The new staging is effective from January 2009)

| Stage | | Definition |
|---|---|---|
| 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 |

*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.

## Salient features of FIGO 2009 Staging
## Approved changes to cervical cancer staging

- Deletion of Stage 0: FIGO has decided to delete Stage 0 from the staging of all tumors, since it is a pre-invasive lesion.

- Stage IIA has been subdivided into IIA1 and IIA2 based on tumor size.

The Expert Committee has also taken into consideration further clinical and investigational recommendations:

- Cervical cancer remains a clinically staged disease; nevertheless, research in the field of surgical staging is encouraged.

- When available, all surgical-pathological findings (such as lympho-vascular space involvement (LVSI)) should be reported to the FIGO Annual Report Editorial Office or in other scientific publications, although not included in the staging system.

- The use of diagnostic imaging techniques to assess the size of the primary tumor is encouraged but is not mandatory.

- Others:
    - For those institutions with access to MRI/CT scanning, radiological tumor volume and parametrial invasion should be recorded and sent to the FIGO Annual Report Editorial Office for data entry and inclusion in the Annual Report.

    - Other investigations (i.e. examination under anesthesia, cystoscopy, sigmoidoscopy, intravenous pyelography) are optional and no longer mandatory.

    - Vaginal carcinoma may occur within 5 years after treatment. A malignancy purely confined to vagina with a sustained complete response in cervical carcinoma is regarded as primary vaginal cancer.

# 5 TREATMENT

## Stage IA1:

If stage IA1 cervical cancer is detected on punch/wedge biopsy it is mandatory to perform a cone biopsy to rule out more invasive disease. Cone biopsy can be obtained with knife, Large Loop or Laser. Following conization the further management options are:

- Extrafascial Hysterectomy only (abdominal/laparoscopic/robotic/vaginal) if LVSI negative in cone biopsy specimen, since the frequency of lymph node involvement is very low and hence lymph node dissection is not required. Ovaries can be preserved in young women and if the histologic type is not adenocarcinoma[14]. *Grade B Recommendation.*

- Modified Radical hysterectomy or Trachelectomy (if fertility preservation is required) + pelvic lymphadenectomy if LVSI positive in cone biopsy specimen

## Stage I A1

Stage IA 1 (diagnosed on cone biopsy) →

- Type I Extrafascial hysterectomy
- Close observation (If fertility desired and cone margins negative)
- Modified Radical hysterectomy or Trachelectomy + pelvic lymphadenectomy if LVSI
- Brachytherapy alone (No fit for surgery)
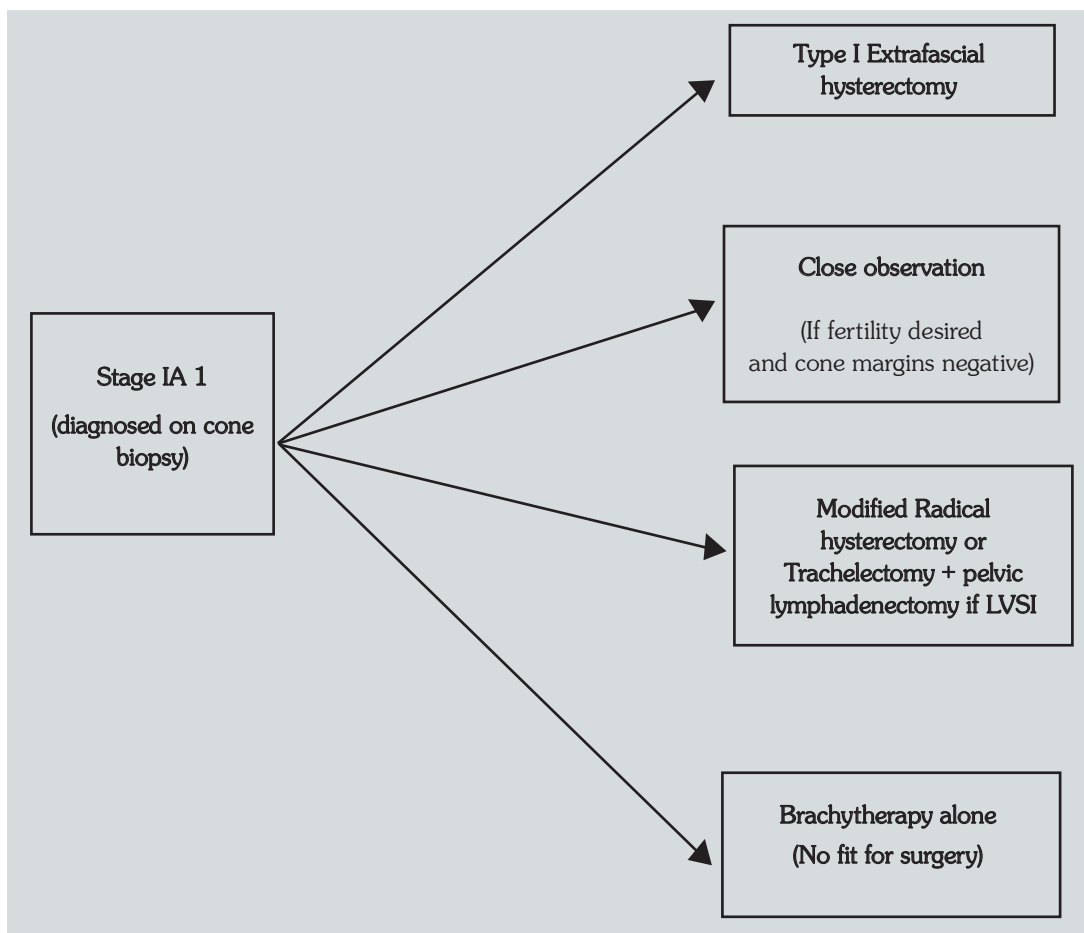
- Repeat conization if the cone margins are positive and fertility preservation is required

- Regular follow up if fertility preservation is required and LVSI negative in cone biopsy specimen and the cone margins are free of disease. ***Grade B Recommendation.***

- Radical Brachytherapy with low dose rate / high dose rate. Total doses: 65- 70 Gy to point A (LDR equivalent) One or 2 intracavitary insertions may be considered up to a dose of 100-125 Gy vaginal surface dose or with HDR (LDR equivalent) in women who are not fit for surgery [15].

## Stage I A2
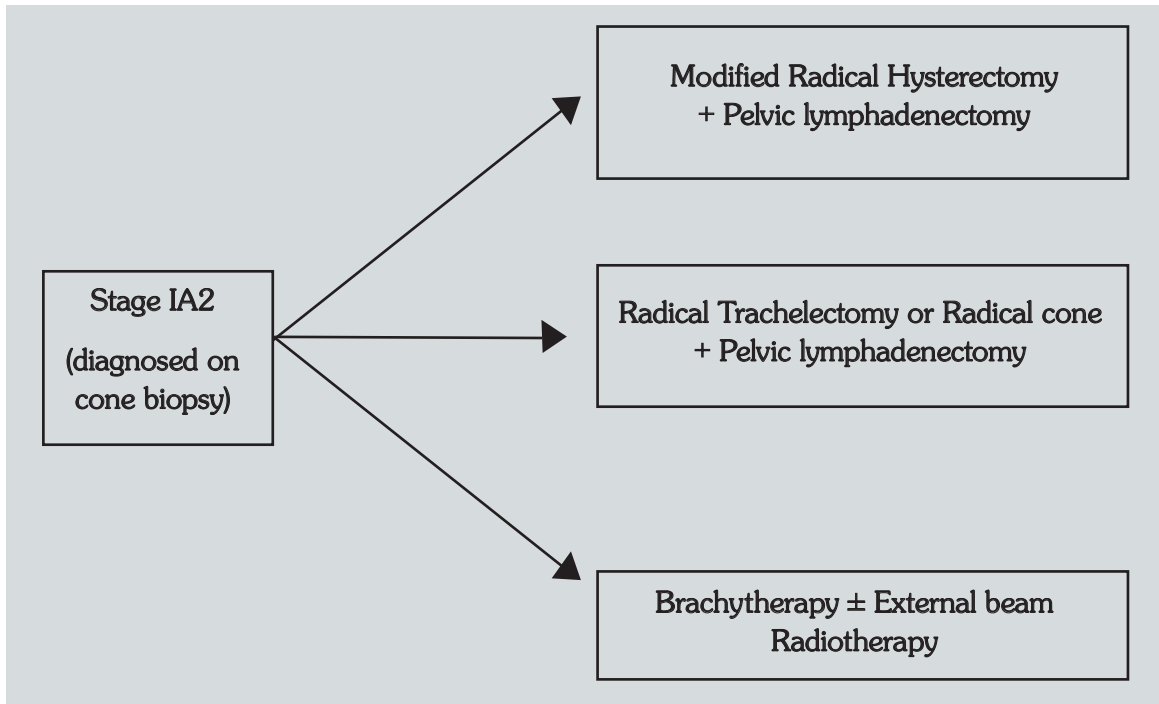


Stage IA2: The treatment options are

- **Modified Radical Hysterectomy + Pelvic lymphadenectomy**

Removal of entire uterus, upper third vagina, bilateral parametria, medical half, uterosacral half, utero-vesical ligaments. Bilateral salpingo-oophrectomy is discretionary depending on the patient's age and histological type of the tumour. The common iliac, external iliac, internal iliac and obturator groups of lymph nodes should be removed from either side.

- **Radical Trachelectomy or Radical cone + Pelvic lymphadenectomy**

In young women with cervical cancer, who are desirous of child bearing, in a select group of patients with tumour size ≤2 cm, and negative pelvic lymph nodes no LUSI, marginsneg radical trachelectomy may be done. Pelvic lymphadenectomy should always precede radical trachelectomy.

- **Radiation Therapy:** Radical intracavitary radiotherapy or intracavitary with external pelvic irradiation may be considered in women who are not fit for surgery.

## Stages IB and IIA

Stages IB1 and IIA1
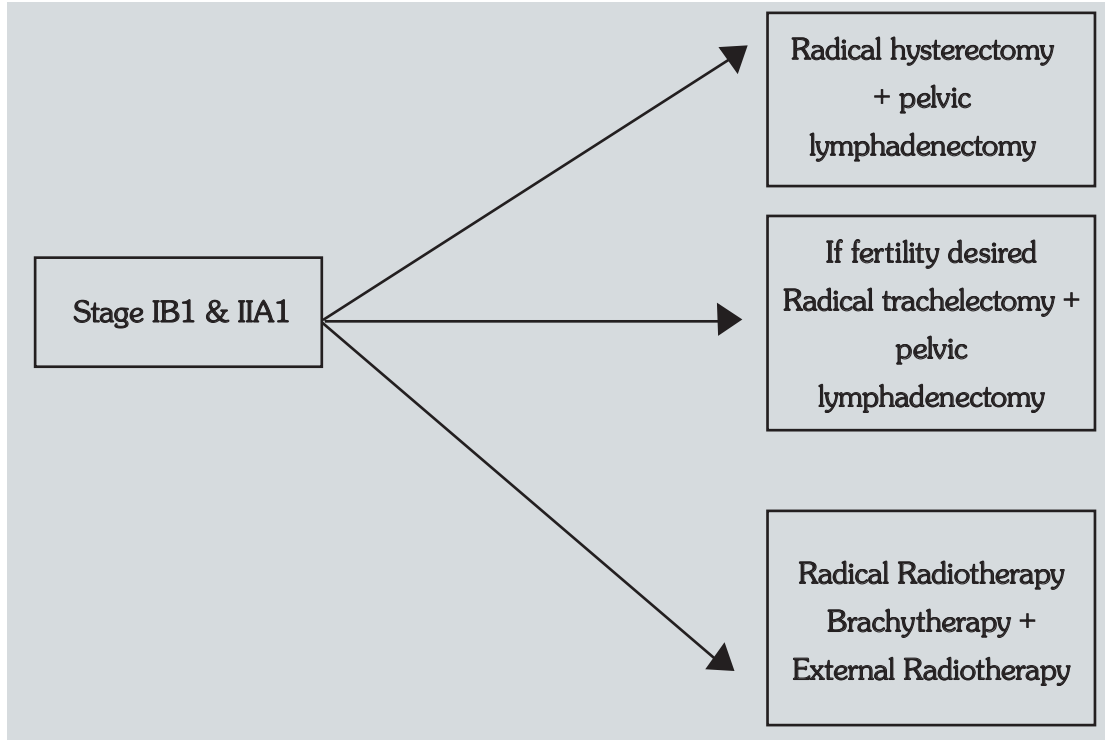


Stage IB1and IIA1:

- Similar cure rates are obtained with radical surgery or radiotherapy for stages IB1 and IIA1 carcinoma of the cervix. However, the long term complications profiles are different for radiation therapy and surgery alone. *Grade A Recommendation.*

- The choice of treatment depends upon the age of the patient, desire to preserve ovarian function, co-morbid conditions, associated gynaecological conditions requiring surgery, facilities and expertise available and the patient's wish

The treatment options are:

- Radical hysterectomy (type III) with pelvic node dissection
  - Para-aortic lymph node assessment during surgery
- Radical trachelectomy + pelvic lymphadenectomy If fertility desired
  - Only for stage IB1, less than 2cm tumor with negative lymph nodes
- Radical Radiation Therapy
  - Consist of external beam radiotherapy and brachytherapy. External-beam pelvic irradiation (40-50 Gy in 4-5 weeks) combined with intracavitary applications, which together delivers the dose of equivalent to 80Gy to point A. Concomitant cisplatin chemotherapy may be added to radical radiotherapy for stage IIA1.

Stages IB2 and IIA2
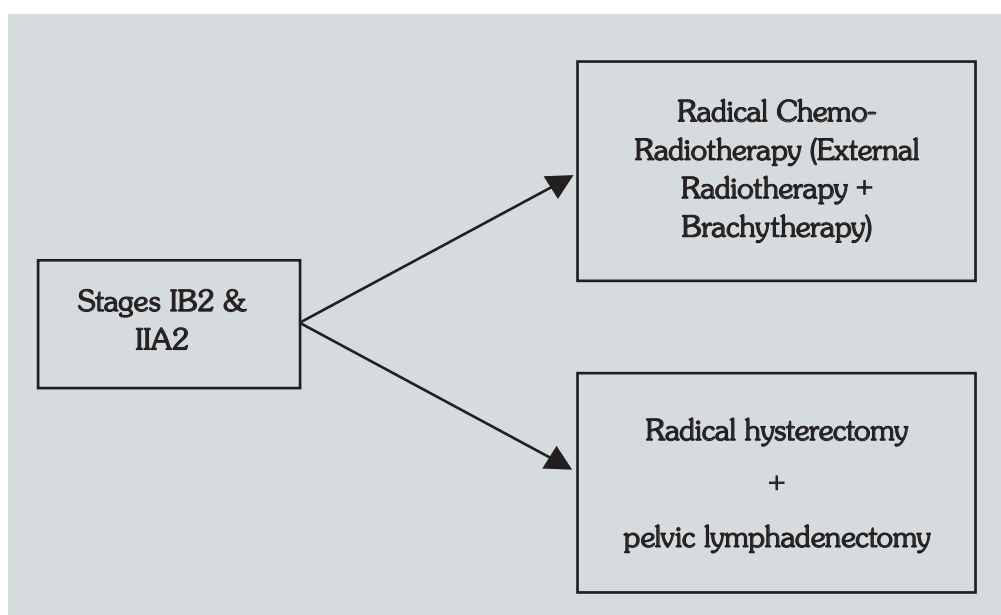


- Stage IB2 and IIA2:

The treatment options include concomitant chemo-radiation (Radiation therapy + Weekly Cisplatin) or radical hysterectomy and lymphadenectomy.

- Radical Radiation Therapy

  - Radical Radiation Therapy consists of external radiotherapy and brachytherapy. External-beam pelvic irradiation (40-50 Gy in 4-5 weeks) combined with intracavitary applications, which together delivers the dose of equivalent to 80Gy to point A.

  - Inj. Cisplatin 40 mg/M² with appropriate hydration weekly during external radiotherapy.

- Radical hysterectomy (Type III) and bilateral pelvic lymphadenectomy.

  - Removal of entire uterus, upper third vagina, bilateral parametria, uterosacral, utero-vesical ligaments and bilateral pelvic lymph nodes. Bilateral salpino-oophrectomy is discretionary.

  - Para-aortic lymph node assessment during surgery

## Adjuvant treatment after Radical surgery

Adjuvant therapy after Radical Surgery
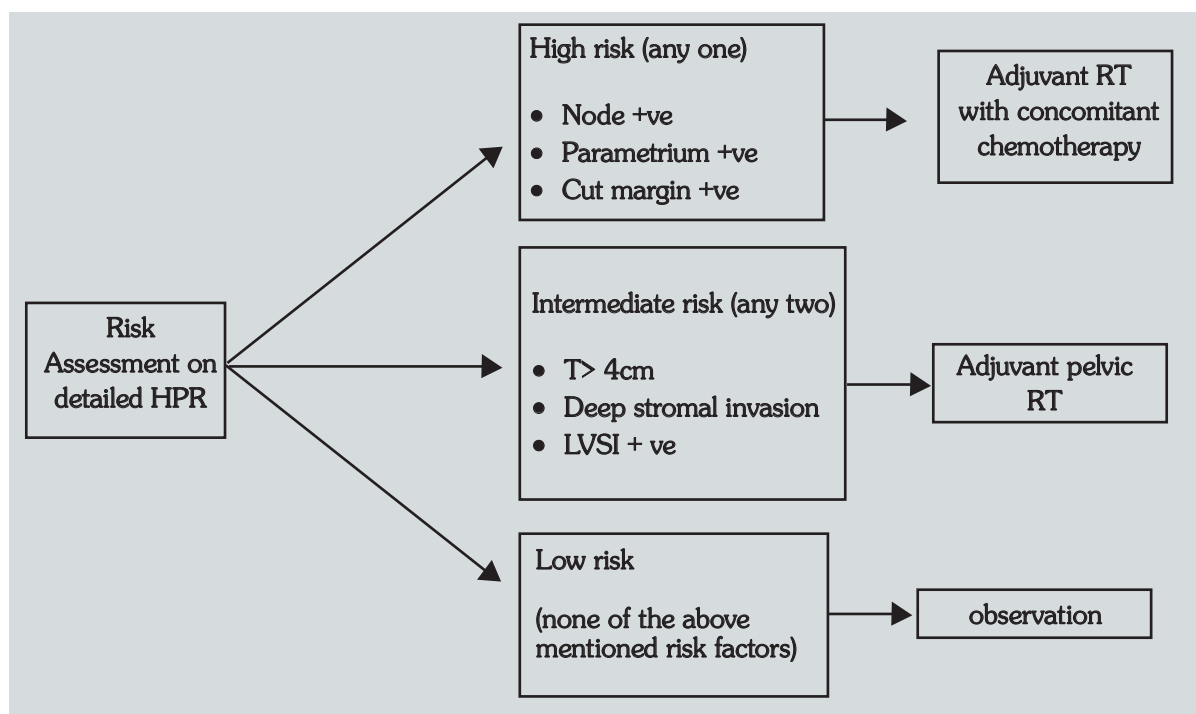


- **High Risk:**

Patients with positive nodes, positive parametria, or positive surgical margins are at increased risk of recurrence. Adjuvant chemo-radiation with external pelvic radiation therapy (45- 50 Gy @ 1.8 – 2 Gy per fraction + / - vaginal brachytherapy boost) and concurrent weekly cisplatin chemotherapy is recommended *if any one of the above factors* is present in the final histopathology[16]. *Grade A Recommendations.*

- **Intermediate Risk:**

Lymphovascular Space involvement (LVSI), deep cervical stromal invasion or tumor size more than 4 cm have increased risk of recurrence. Adjuvant pelvic radiation therapy is recommended *if at least any two of the above factors* are seen on final histopathology. Adjuvant whole pelvic irradiation (45- 50 Gy @ 1.8–2 Gy per fraction +/- vaginal brachytherapy boost) reduces the local failure rate and improves progression-free survival compared with patients treated with surgery alone[17]. *Grade A Recommendations.*

- **Low risk:**

No adjuvant therapy recommended *if none of the factors mentioned in high and intermediate risk groups* are present in final histopathology after adequate surgery.

- For patients undergoing inadvertent hysterectomy/simple hysterectomy for invasive cervical cancer, completion surgery may be considered. However, immediate second surgery is not practical, so these patients should be considered as high risk and treated with adjuvant chemo-radiation. If compliance to concomitant chemo-radiation is compromised because of medical and social reasons, radiotherapy alone is an acceptable alternative.

## Stage IIB and III
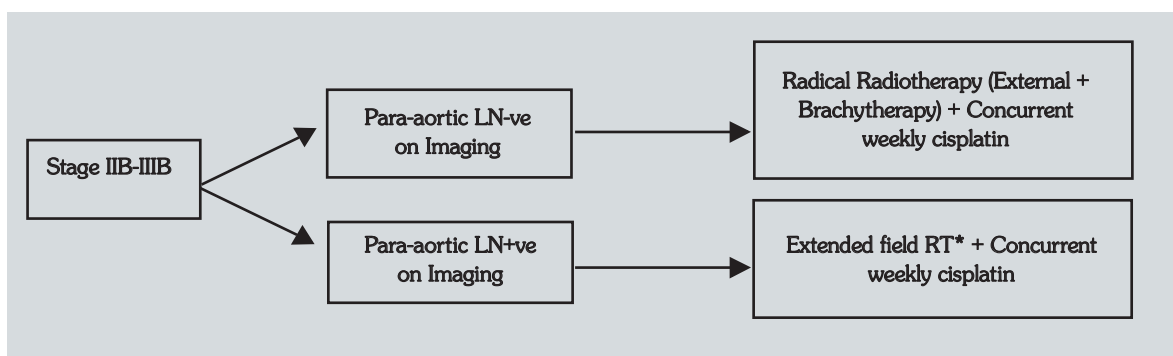


Stage IIB and III: The options are

- Radiotherapy remains the mainstay of treatment. Addition of concurrent chemotherapy reduces the metastasis and improves the survival. *Grade A recommendations*

- Radical radiotherapy is usually a combination of external beam pelvic radiation and intracavitary brachytherapy (Low dose rate/ High Dose rate / Pulse dose rate)

- External beam radiation therapy could be conventional 2dimensional or 3dimensional conformal techniques.

- In all patients treated with radical intent, brachytherapy should be an essential component.

- Adequate and optimal total (external + Brachytherapy) doses to Point 'A' (80–90 Gy) depending on the stage, response and doses to limiting normal structures should be achieved.

- Planned radical radiation / concomitant chemo-radiation should be completed within 8 weeks without significant treatment breaks, because prolonged overall treatment time result in poor outcome. *Grade C recommendations*

- Concurrent chemotherapy with Cisplatin 40 mg/m2 weekly during the course of external radiation is recommended provided adequate renal functions / creatinine clearance is present.

- Patients with positive common iliac or para-aortic nodes (up to 3 cm in maximum dimensions) may be treated by extended field radiation with or without concurrent chemotherapy. *Grade C Recommendations*

## Stage IV
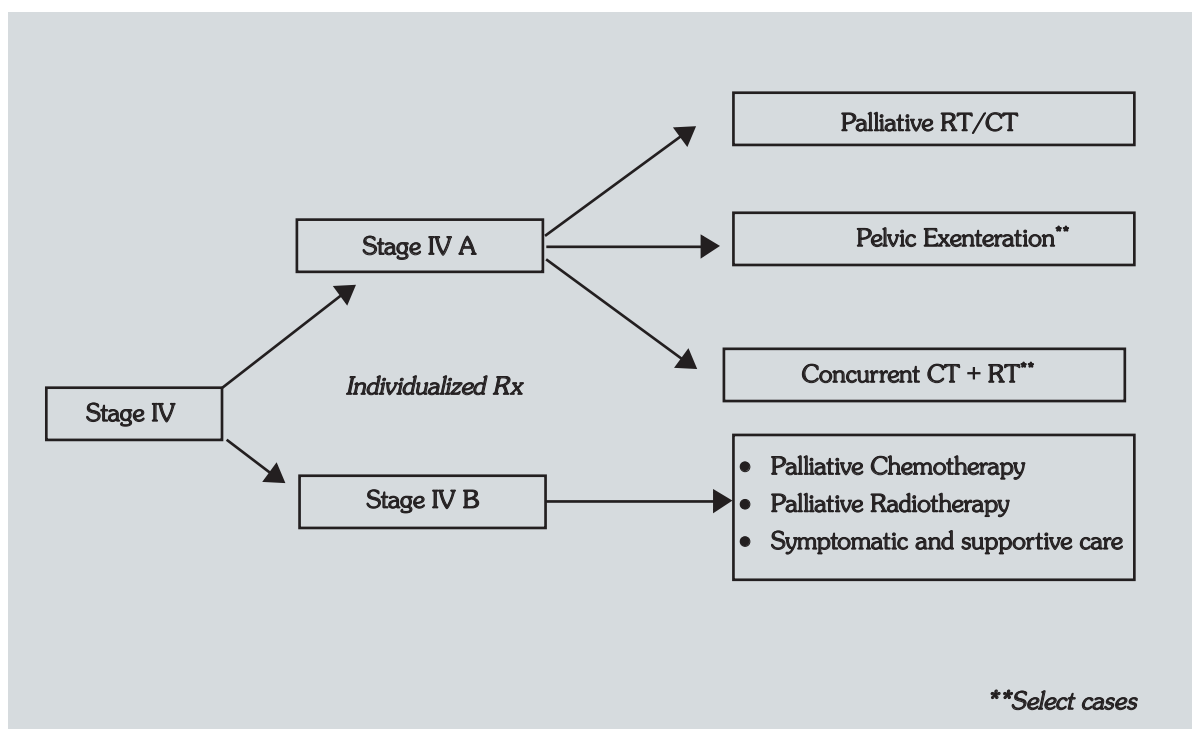


### Stage IVA:

- Majority of stage IVA patients has poor general condition and extensive local disease in our setting and are best treated with palliative radiation therapy / chemotherapy.

- Major symptoms which can be palliated are vaginal bleeding, profuse discharge, low backache due to local disease etc.

- Hypo-fractionated palliative external beam radiation therapy regime of 30 Gy in 10 fractions over two weeks or 30 Gy / 3# / 60 days (10 Gy / every month x 3#) is generally used and in few patients who respond very well, this is followed by brachytherapy (LDR / HDR).

- Palliative chemotherapy has been detailed in the management of FIGO stage IVB section.

### Stage IVB:

- Patients with metastatic disease are not curable and the intent of treatment is symptom control and prolongation of survival.

- Radiation therapy can be used for palliation of symptoms due to central disease or symptomatic distant metastasis including skeletal metastases, enlarged para-aortic or supra-clavicular nodes, and brain metastases.

- Palliative radiotherapy should be given via larger fractions over shorter periods of time than conventional radical courses of treatment.

- Patients with poor performance status are not candidates for palliative chemotherapy, in general.

- Palliative chemotherapy is generally used for extra-pelvic disease / recurrences or for pelvic recurrences without previous irradiation. There is some evidence that it may palliate symptoms and/or prolong survival in this setting. *Grade B recommendation*

- Choice of chemotherapy:

  - Combination regimens have generally been shown to improve response rates (RR) and progression-free survival (PFS) but not overall survival (OS) compared to single agent cisplatin[17]. Most commonly used regimen is paclitaxel and either cisplatin or carboplatin[18]. Although there is no randomized phase III evidence for carboplatin, there are several retrospective analyses and prospective non-randomized studies that indicate equivalent efficacy[19,20]. Therefore it is preferred over cisplatin (for which there is a randomized phase III trial[18] because of ease of administration and better tolerability with respect to emesis, renal toxicity, ototoxicity, etc. *Grade B recommendation*

  - Another regimen that has been tested in a randomized phase III trial is topotecan plus cisplatin that was shown to be superior to single agent cisplatin with respect to RR, PFS and OS[21]. However it is not the preferred standard because of its unfavorable toxicity profile, including myelosuppression and gastrointestinal toxicity. A recent phase III trial compared 4 platinum doublets (cisplatin + either of the following: paclitaxel, topotecan, gemcitabine and vinorelbine ). There were no statistically significant differences in OS but there was a trend to superiority of cisplatin-paclitaxel in RR, PFS and OS[22]. *Grade B recommendation*

  - Other agents uncommonly used as second line palliative chemotherapy include vinorelbine, bevacizumab, irinotecan, ifosfamide and 5-FU.

  - To summarize the choice of palliative chemotherapy regimens: Paclitaxel plus carboplatin or single agent cisplatin.

  - In patients in whom peripheral neuropathy is a concern, gemcitabine-platinum is an acceptable alternative. Carboplatin is substituted for cisplatin in many regimens by most clinicians. Generally 4-6 cycles of chemotherapy are used.

- Response evaluation: Patients on palliative chemotherapy should be evaluated for disease response clinically (including symptomatic benefit) and radiologically as appropriate after every few cycles of chemotherapy.

- Patients not suitable for palliative radiotherapy or chemotherapy, symptomatic and supportive care should be offered. Patients should also be referred to a palliative care team, if accessible, early in the course of metastatic disease. Counseling and symptom control are some of the important components of palliative care for these patients.

## Recurrent Pelvic Disease
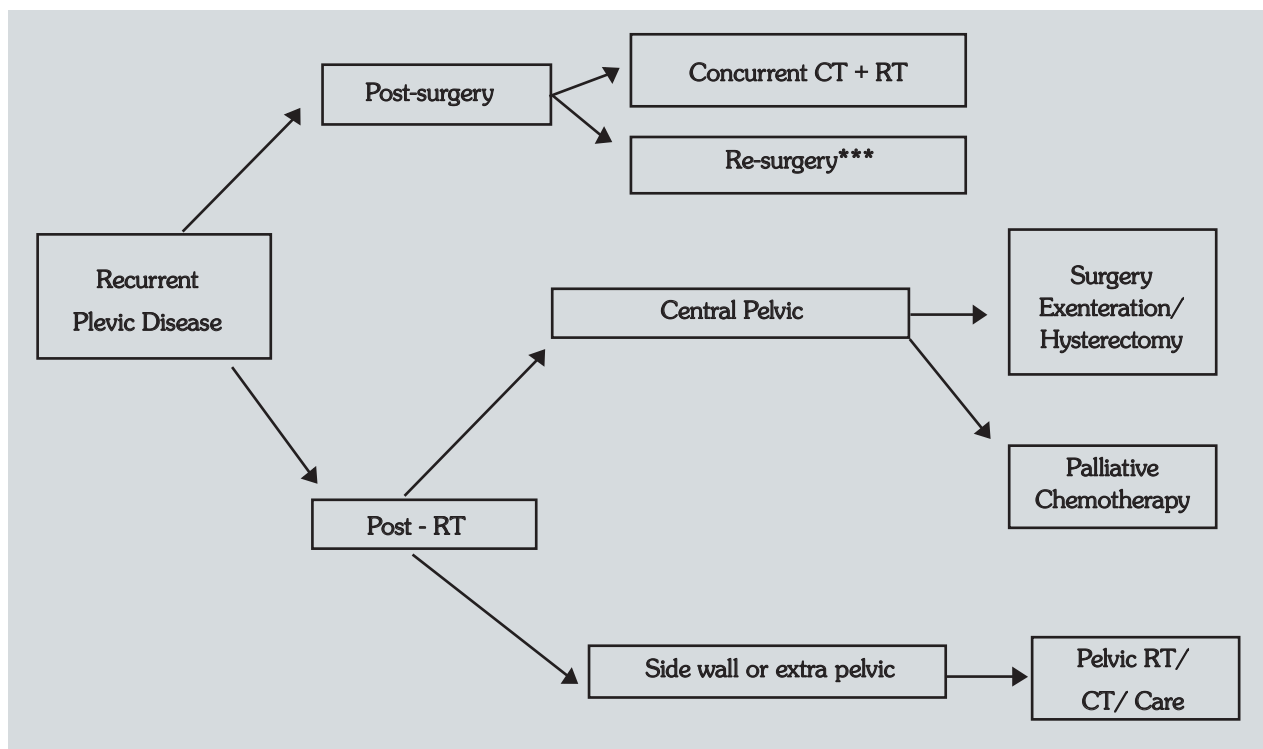


- Relapse in the pelvis following primary surgery may be treated by radical radiation therapy with concomitant chemotherapy.

- Radical irradiation (with concurrent chemotherapy) may cure a substantial proportion of those with isolated pelvic failure after primary surgery depending on the extent of disease.

- Radiotherapy is usually a combination of external beam pelvic radiation and appropriate intracavitary/ interstitial or combination brachytherapy (Low dose rate/ High Dose rate / Pulse dose rate) depending on the available expertise. However, referral for interstitial brachytherapy to appropriate centers with expertise and experience is encouraged wherever feasible.

- Radiation treatment planning and dose prescription should be similar to locally advanced cervical cancer protocols. Patient not suitable for brachytherapy after external beam radiation, further external radiation boost with small fields up to a dose of 64 – 66 Gy.

- For Post RT central recurrence, pelvic exenteration (particularly if a fistula is present) in selected patients without pelvic sidewall involvement may be offered.

- This surgery should be undertaken only in centres with facilities and expertise and only by teams who have the experience and commitment towards management of post-operative short and long-term rehabilitation of these patients.

- Palliative Chemotherapy has limited efficacy in pelvic recurrences that have been heavily irradiated earlier. It should only be used in highly selected patients with this presentation on an individualized basis. *Grade C Recommendation*

- The choice of chemotherapy schedules and frequency is similar as detailed in treatment of FIGO IV B section.

# 6 SPECIAL SITUATIONS

## 6.1 Pregnancy

### Stage I A1
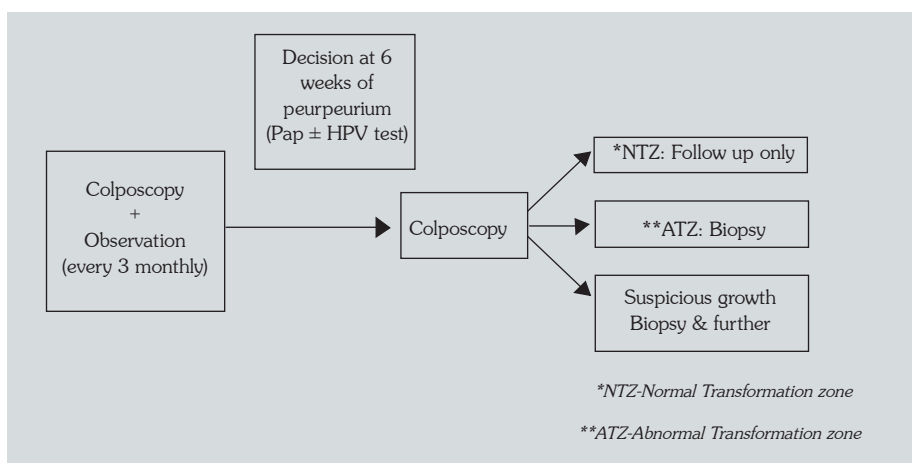


- Colposcopy for IA1 and observation every 3 months
- Anytime suspicious lesions should be biopsied

### IB1 – IIA1
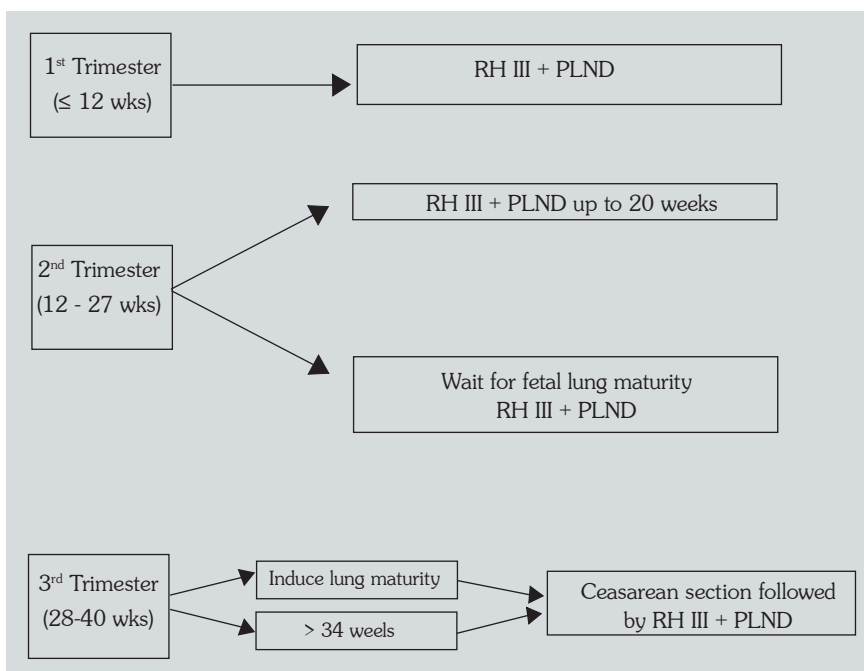
**IIA2 – IIIB**
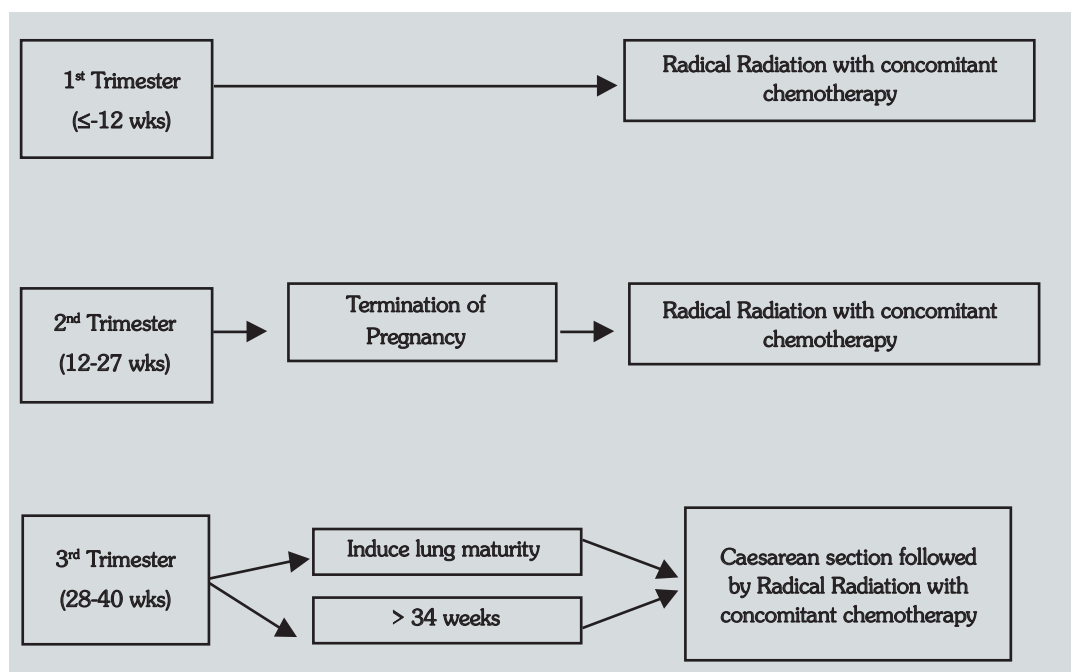


- Either surgery or radiotherapy is used, depending on the stage of the disease in the first trimester.

- In the third trimester, definitive treatment is usually delayed until the foetus is mature.

- A multidisciplinary team approach is essential in making decisions with every effort made to maximize the treatment.

## 6.2 -Retroviral Positive:

In patients with retroviral positive, there is higher incidence of *in situ* and invasive cervical cancer. In general, cervical cancer is diagnosed at an earlier age in the retroviral positive patient [23]. Antiretroviral therapy (ARV) reduces AIDS related causes of death by 75%. The medical management of retroviral positive and AIDS patients diagnosed with cervical cancer should follow the general guidelines for the treatment of carcinoma cervix.

Women should be offered curative treatment for cervical cancer according to the stage of disease and the general medical condition, irrespective of their retroviral status. The indication for chemotherapy is tailored to the performance status and immune status of the patient. No chemotherapy is recommended if the CD4 count is below 200 cells/mm$^3$. Myelosuppression should be carefully monitored. During treatment, patients require close monitoring in the same manner as in the retroviral negative setting. Retroviral positive patients are particularly at risk of developing increased acute and possibly long term toxicity from radiation and, especially, from concurrent radiation and chemotherapy [23].

## 6.3: Neuroendocrine tumor

Neuroendocrine tumor comprises of family of tumors ranging from well differentiated neoplasms (carcinoids and atypical carcinoid) to high grade neuroendocrine carcinomas (small cell and large cell) having a common origin from the diffuse neuroendocrine cell system[24]. The biology, clinical outcome and treatment of high grade neuroendocrine carcinomas are different from well differentiated tumors. Most common neuroendocrine of cervix (NCC) is small cell carcinoma, comprising around 1-5% of all cervical

neoplasms[25]. Behavior of small cell carcinoma cervix (SCCC) is similar to small cell carcinoma lung so that lymph node spread is very common, propensity of vascular invasion, tendency for hematogenous dissemination at relapse. Large cell carcinoma cervix though uncommon has similar clinical features and behavior compared to SCCC.

## Epidemiology

Risk factors for NCC have not been elucidated. HPV-18 seems to be associated with this tumor in various reports[26]. Unlike small cell carcinoma of lung its association with smoking is not yet proven. Incidence of neuroendocrine carcinoma seems to be on rise probably attributed to increased diagnostic recognition.

## Clinical features

Though there is wide range of ages involved, this most commonly presents in fifth decade. Patients usually present with abdomino-pelvic symptoms such as vaginal bleeding or discharge, pelvic pain, or pelvic pressure. Only few asymptomatic patients are detected with abnormal Pap smear. Patients may rarely present with paraneoplastic syndromes like cushing's syndrome, SIADH, carcinoid syndrome and other neurological disorders. Patients may also present with metastatic disease at presentation and most common sites of metastasis are liver, adrenals, bone, bone marrow, and the brain.

A pelvic mass is most common finding on physical examination. On examination only it is impossible to distinguish NCC from squamous cancer of cervix.

## Diagnosis and staging

A diagnostic biopsy with histopathological examination and immunohistochemistry are mandatory to diagnose neuroendocrine carcinoma. It is important to differentiate it from other small blue cell tumors arising in cervix including basaloid squamous cell carcinoma, embryonal rhabdomyosarcoma, and rarely lymphoma.

Neuroendocrine carcinomas are staged similar to squamous cell cervical cancer. Since neuroendocrine carcinomas are associated frequently with disease outside cervix so all patients should undergo computed tomography (CT) of the chest, abdomen, and pelvis for assessment of locoregional disease as well as distant spread. Since metastatic disease accounts for 20-40% of cases in different series so some guidelines suggest doing PET-CT though prospective evidence for the same is not available [27]. In view of very low incidence of brain metastasis in upfront setting CT head is not required in absence of symptoms or lung metastasis.

## Prognostic factors

Advanced stage is the most consistent and probably strongest prognostic factor in most of the studies. Other prognostic factors are tumor size, presence and number of lymph node metastasis, pure small cell histology and smoking[28]. Lymph node involvement is present in around 50% of patients at presentation. In a retrospective series(n=188) 5-year disease-specific survival in stage I-IIA, IIB-IVA, and IVB disease was 36.8%, 9.8%, and 0%, respectively (P<.001)[29].

## Treatment

For the sake of simplicity treatment can be divided according to extent of the tumor. Disease can be divided into limited stage resectable disease, non metastatic locoregionally advanced unresectable disease and metastatic disease. Also most of the strategies for treatment of small cell cancer of cervix have been extrapolated from small cell cancer lung.

## Limited stage resectable (stage I-IIA)

Since, there is no evidence showing superiority of either of surgery (radical hysterectomy with regional lymphadenectomy) or primary chemo-radiation. So either of them can be used to treat limited stage resectable disease. Post surgery as in lung cancer adjuvant chemotherapy should be given in all cases.

Post operative chemotherapy has been shown to be associated with increased survival in various retrospective studies. Out of various chemotherapy regimens used in these studies EP regimen is preferred over other regimens because of less toxicity. There is no role adjuvant radiation as no advantage has been seen in various retrospective studies in terms of recurrences or survival. Some guidelines recommend upfront surgery for tumor size less than 4 cm and neoadjuvant chemotherapy or chemoradiation for tumor size more than that but prospective evidence for this stratification is lacking[27]. Data for neoadjuvant therapy is sparse so treatment should be individualized.

### Loco-regionally advanced disease

For advanced unresectable disease definitive chemoradiation like small cell lung cancer is recommended. Hoskin et al. reported results at British Columbia cancer agency for SCCC treated between 1988-2002 treated with platinum based chemoradiation and showed clinical stage as the only independent predictor of outcome. Distant failure rates were 28% with their regimen as compared to 13% local failure rates.

### Metastatic disease

For patients with metastatic disease or recurrent disease patients should be treated with EP or VAC based chemotherapy as in small cell neuroendocrine carcinoma of lung.

### Conclusion

Though data regarding treatment strategy of NCC is sparse but multimodality therapy with chemotherapy, radiotherapy and surgery seems to improve outcome. More prospective data is needed for this rare but potentially curable tumor.

### 6.4 -Anaemia

Low hemoglobin level is frequently observed in these patients because of prolonged vaginal bleeding, poor nutrition, advanced disease, bone marrow toxicities during treatment and lack of supportive care. A low hemoglobin level during radiotherapy/ chemo-radiotherapy reflects lower local control and survival [30].There is not enough evidence to recommend routine use of agents stimulating erythropoiesis[31].

# 7 FOLLOW-UP STRATEGIES

After completing the treatment patients require regular clinical follow-up to detect possible recurrence and evaluate the potential complications.

1. Since the recurrence is common during first two years following treatment. Patient should follow once in four months for first two years and every six months for 3 years and yearly thereafter.

2. Role of annual PAP smear is controversial. In absence of symptoms it is not warranted. Local recurrence has to be established histologically and should not be based on PAP cytology alone.

3. Evaluation with radiology, cystoscopy, recto-sigmoidoscopy, chest x-ray, CT scan may be done if clinically indicated, however general history and physical examination is recommended at each follow-up visit.

4. Patients should be educated regarding symptoms suggestive of recurrence and metastasis for early diagnosis of recurrence.

5. The narrowing of vaginal causing dyspareunia and post coital bleeding. Patient should be educated to use dilator or resume intercourse to avoid this complication.

# 8 RESEARCH ISSUES

1. Treatment Related Complications and Outcome in Indian Women

2. Quality of Life Issues

3. Cervical Cancer Screening Program

4. Prevention: HPV Vaccination

5. Anti HPV Therapeutics and Targeted Delivery.

6. Incorporation of neoadjuvant chemotherapy in primary treatment

7. Role of adjuvant chemotherapy following chemo-radiation

8. Cervical cancer stem cell

9. Minimal access surgery

10. Biomarkers and Genomics for prognostication

11. Determination of node metastasis by newer techniques

# 9 APPENDIX

## Appendix – A

## BIOMARKERS AND CERVICAL CANCER

The biomarkers offer great potential for improving management of cancer at every point from screening and detection, diagnosis, staging, prognosis to assessment of treatment response. A significant advancement in understanding causes of cervical cancer and identification of several biomarkers have been achieved for its early diagnosis, prevention and treatment.

## 1. Primary Biomarkers:

**i. HPV DNA testing as the primary biomarker for early detection of precancer lesions and triaging.** Direct detection of HPV DNA in cervical specimens may offer an alternative or complementary to population-based cytological screening. It has been reported that HPV test results are more sensitive than Pap smears in detecting high-grade lesions in older women[32-33]. A population-based study demonstrated for the first time the impact of single round of HPV DNA testing as an effective primary screening tool with better efficacy than other conventional methods [34]. In a large population-based cytological screening from Costa Rica, a cut-off point of 1.0pg/mL using the second generation assay allowed sensitive detection of cervical high-grade lesions and cancer, giving a seemingly optimal trade-off between high sensitivity and reasonable specificity rates for this test. PCR detection of HPV DNA by L1 consensus primers and typing by HPV type-specific primers should be performed to detect the presence of high-risk HPVs. Most widely used My9 and MY11 consensus primers are capable of detecting about 27 HPV types which include all 15 High Risk HPVs (HPV 16, 18, 31, 35, 39, 45 etc) and 6 low Risk-HPVs[35]. Since most HPV infections in women are transient and only a minority of women infected with HPV develops persistent infection that may evolve into squamous intraepithelial lesions, triaging of women infected with HR-HPV and management of co-factors such as inflammation and infection of RTIs is recommended. Studies also support the potential utility of HPV testing for effective triaging of Pap smears of atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGUS) and therefore have a potential role in primary screening of populations in which pap smears have been inconclusive. DNA probes of high-risk HPV types in different formats have been fully validated as primary screening tests, as secondary triage tests and as a prognostic marker following treatment of high grade squamous intraepithelial lesions (HSIL). They consistently showed significant superiority over the conventional Pap smears.

**ii. HPV E6 and E7 protein detection in the severe dysplastic and invasive carcinoma cases.** Since two early genes E6 and E7 are the two main viral transforming genes that are invariably retained in almost all cervical cancers, detection of these two viral oncoproteins can serve as important biomarkers of severe dysplastic and invasive cervical cancers and progression of the disease. HPV E6 and E7 oncogenes play an essential role in HPV-induced carcinogenesis by interfering with two essential tumor suppressor genes

p53 and Rb that regulate normal cellular events and are possible protein biomarkers for early detection of cervical cancer. Studies show that detection of E6/E7 mRNA expression could predict the risk of cervical cancer better than HPV DNA testing[36] and currently the commercially available mRNA-based assays (e.g., NucliSENSEasyQ HPV Test and APTIMA HPV mRNA Assay) are being used. Arbor Vita Corporation has developed a rapid diagnostic test, "AV Avantage HPV E6 test" in collaboration with PATH (the Program of Appropriate Technology in Health) with FDA approval expected in 2013. AV Avantage HPV E6 test uses a high-affinity monoclonal antibody for the detection of E6 oncoprotein from high risk HPV-16, -18, and -45 responsible for approximately 90% of cervical cancers.

**i. Viral load and Integration.** There exists a close link between HPV viral copy number and integration of viral genome into the host cell and is considered as a risk factor for the progression of pre-cancer to invasive cancer [37]. The significantly higher HPV load detected in women with high-grade cervical dysplasia, as well as the dramatic difference in the load after surgical removal of the lesion, suggest that HPV load is a possible prognostic marker of high-grade squamous intraepithelial lesion. Integration of the viral DNA to host cell genome is yet another biomarker as persistent HPV infection leads to integration of viral DNA into the host cell genome, leading to tumorigenic transformation of cervical epithelium.

## 2. Secondary Biomarkers

A number of molecular markers have been found to show an early sign of alteration at the onset of disease which may be useful in predicting the disease course at an early stage.

### Tumor suppressor genes and proto-oncogenes

i.   **p53** has been found to be deregulated with the progression of lesions, suggesting that p53 abnormality is an early event in cervical carcinogenesis. The E6 protein of oncogenic HPV types has been shown to complex with p53 and targets it for rapid degradation. As a consequence, p53's growth-arrest and apoptosis-inducing activities are abrogated. This suggests the potential importance of the E6 - p53 interaction for therapeutic intervention.

ii.  **p16,** the cyclin D/cdk inhibitor is overexpressed as the lesions proceed to a more aggressive one. This tumor suppressor p16INK4A plays an important role in regulating the cell cycle and is overexpressed in the presence of the HPV E7 oncoprotein. Several studies reported p16INK4A as a useful diagnostic marker for squamous and glandular epithelial dysplasia in the uterine cervix 38-39 and a valuable surrogate marker for high risk and malignant cervical lesions in the presence of HPV40. Furthermore, expression of p16INK4A appears to correlate with the degree of cervical neoplasia41-42. A recent study showed that a p16INK4A immuno-cytochemical assay has better specificity than HPV testing to predict underlying high-grade dysplastic lesions43. Currently, clinical trials are underway to assess the diagnostic and prognostic value of p16INK4A expression in atypical glandular cells and low-grade squamous intraepithelial lesions of the cervix.

iii. **c-fos protein** specifically shows exclusive high expression with the increasing severity of lesion and in cancer. The transcription factor AP-1, which is composed of heterodimers of members of the c-Jun and c-Fos families, regulates various cellular processes such as enhanced proliferation, apoptosis, and tumor metastasis. c-fos acts as a tumor promoter, and its upregulation causes cellular transformation and when c-fos binds to c-jun contributes to the potentiating of malignancy.

iv.  **Fra-1** is expressed in normal cervical tissue and its expression was diminished as the lesion progressed from precancer to cancer. Thus in cervical cancer it acts like a tumor suppressor gene 44.

v.  **p50 subunit of NF-kB** shows enhanced expression in high grade cervical lesions and changes in relation to disease progression 44.

vi. NOTCH 1 family of proteins are found to be highly expressed from CIN III onwards. Thus, Notch1 exerts specific protective effects against HPV-induced transformation through suppression of E6/E7 expression, and down-modulation of Notch1 expression is likely to play an important role in late stages of HPV-induced carcinogenesis45.

vii. **R-bprotein** has been found to be deregulated in poorly differentiated carcinoma, suggesting its important role in differentiation. pRB is a negative regulator of the cell cycle that normally prevents S-phase entry by associating with the E2F family of transcription factors. E7 binding to pRB release E2F, irrespective of the presence of external growth factors leading to the expression of proteins necessary for DNA replication[46]

viii. **Telomerase** activation is a relatively early event in cervical carcinogenesis and mostly correlated with the grade of cervical lesion, HR-HPV status (HPV 16 and 18 subtypes) and clinical staging. Upregulated hTR and hTERT subunits of telomerase have also been observed in cervical cancers [47]

ix. **Ki-67** is a nuclear protein that is expressed during all active phases of the cell cycle, and its expression is used to determine the cell proliferation status [48]. In cervical intraepithelial neoplasia (CIN), Ki-67 expression is increased in the upper layers of cervical epithelium compared to normal cervices [48]. Several studies have also suggested that Ki-67 can be used as an independent prognostic marker to identify women with high risk for progression and/or recurrence of cervical squamous precancerous lesions [49].

x.  **E cadherin, cadherins are** glycoproteins of 120 to 130 kDa that are involved in the cell adhesion and is considered as an important biomarker for tumor development [50,51]. The squamous cells of cervix epithelium are strongly attached to each other and to the basement membrane through a large number of adhesion molecules. Thus, E-cadherin is one of the key molecules of adhesion. The decrease or loss of expression of these molecules can be correlated with aggressive behavior and progression of cancer. The decrease in the expression of E-cadherin seems to be a useful parameter in evaluating the potential for malignancy of cervical cancer[50].

### Potential serum markers

i.  **SCC (Squamous cell carcinoma antigen)** For cervical cancer, the discovery of useful serum biomarkers for its early detection has been a priority nowadays. Such tumor markers are the molecules arising due to presence of the tumor, which can appear in the surrounding tissue, and then within the blood and excretions. Diagnostic serum markers for cervical cancer in clinical use are SCC antigen (squamous cell carcinoma antigen)52.

### Cell Adhesion Matrix proteins

i.  **Cell adhesion matrix proteinsCD44,** and its variant forms, are integral membrane proteins that have been implicated in tumorigenesis. They act as both a lymphocyte homing mechanism and cell adhesion molecule, as well as being involved with tumor growth, spread, and invasion53. CD44 is generally used as an epithelial cancer stem cell marker and thus provide novel approaches to the diagnosis and treatment of cancer.

## MiRNA

i.   Micro ribonucleic acids (miRNA) is released and circulated in the blood of cancer patients. Changes in the levels of circulating nucleic acids have been associated with tumor burden and malignant progression. The area of metastasis-associated miRNA markers in relation to oncogenesis is expanding rapidly and these markers have recently been referred to as "metastamirs". miRNA can act as a tumor suppressor as well as an oncogene. This emphasizes the potential application of miRNAs as biomarkers, In the past decade, huge number of publication on the potential use of circulating nucleic acids for cancer screening, prognosis and monitoring of the efficacy of anticancer therapies has emerged. Mir 21 is upregulated in solid tumors and participates in oncogenic signaling. MiR-21 is transcriptionally induced by AP1 which is essential for HPV transcription. Another miRNA, miR-29 restrains cell cycle progression and induce apoptosis and promotes malignant transformation induced by HPV 54

## Appendix-B

## REPORTING FORMAT FOR CERVICAL CANCER IN CONE BIOPSY HISTOPATHOLOGY EXAMINATION

**GROSS EXAMINATION:**

**Specimen type:**                                                       LEEP / CONE

        Dimensions                          ......x..... x......mm

        Resection margins                :

        Number of sections studied       :

**MICROSCOPY:**

        Description:...............................................................

        .................................................................................

**Diagnosis** (Select one or more as appropriate):

          ☐   **CIN 2/ CIN-3**

        Focuses                                  unifocal / multifocal

        Number of sections involved       **# .....**

        Endocervical glandular involvement   Present / Absent

          ☐   **CGIN (Cervical Glandular Intraepithelial Neoplasia):**   low grade / high grade

          ☐   **Microinvasive Carcinoma\***

        Depth of Invasion                  ...... mm

        Lateral extent of Invasion         ...... mm

          ☐   **Early Invasive Squamous Cell Carcinoma**

        Depth of invasion                 ......mm

        LVSI (Lympho-Vascular Space Invasion)   Present / Absent

          ☐   **Adenocarcinoma-*in-situ***

          ☐   **Early invasive adenocarcinoma**

        LVSI **(Lympho-Vascular Space Invasion)**   Present / Absent

**Resection margin-**

          ☐   Upper resection limit:         Involved / Not Involved

          ☐   Lower resection limit          Involved / Not Involved

          ☐   In case of invasive carcinoma, Deep resection limit:   Involved / Not Involved

*\* Note on Measurement of invasion:*

*Depth of invasion: Measurement is taken from the base of the epithelium (surface or glandular) from which the carcinoma arises, to the deepest point of invasion, as specified in the FIGO classification.*

*If the invasive focus is not in continuity with the dysplastic focus, measure depth from the nearest dysplastic crypt / surface epithelium or from the adjacent non-neoplastic surface epithelium / crypt base.*

*Lateral extent of invasion: The maximum horizontal extent of invasion should be measured in mm.*

*The number of sections showing invasion must be mentioned in the report.*

# REPORTING FORMAT FOR CERVICAL CANCER IN BIOPSY SPECIMEN

**GROSS EXAMINATION:**

**Specimen type:**                                                                    Wedge / Punch

            Number of fragments                                          # .....

            Resection margins

            Size of each fragment in three dimensions

                                                       1.   ...... x ..... x......mm

                                                        2.   ...... x ..... x......mm

                                                        3.   ...... x ..... x......mm

                                                        4.   ...... x ..... x......mm

                                                        5.   ...... x ..... x......mm

**MICROSCOPY:**

            Description: ................................................................

            ......................................................................

            ......................................................................

**Diagnosis**

            Histological types (as WHO classification)

            **LVSI (Lympho-Vascular Space Invasion)**                Present / Absent

            **Presence of associated CIN / CGIN**                         Present / Absent

# REPORTING FORMAT FOR CERVICAL CANCER IN HYSTERECTOMY SPECIMEN

**GROSS EXAMINATION:**

| | |
|---|---|
| **Specimen type:** | Hysterectomy/ Radical Hysterectomy |
| **Tumor site-** | □ anterior □ posterior □ right □ left □ circumferential |
| **Cx. Involvement-** | □ ectocervix □ endocervix |
| **Tumor size-** | ......cm x ..... cm |
| **Tumor description-** | **(colour of tumor, polypoidal, infiltrative, ulcerative):** |
| | ..................................................................................... |
| | ..................................................................................... |

| | | |
|---|---|---|
| **Extent of tumor-** | *stromal invasion / upward extension* | : |
| **Uterine corpus-** | *Dimension, Endometrium, Myometrium* | : |
| **Vaginal cuff-** | *Dimension, Involved or not* | : |
| **Parametrium-** | *Dimension, Involved or not* | : |
| **Other Organs:** | | : |
| | • *Rt. Ovary – Dimension, Pathologic macroscopic findings* | : |
| | • *Lt. Ovary – Dimension, Pathologic macroscopic findings* | : |
| | • *Rt. Fallopian tube – Dimension, Pathologic macroscopic findings* | : |
| | • *Lt. Fallopian tube – Dimension, Pathologic macroscopic findings* | : |
| **Lymph Nodes-** | • *Site* | : |
| | • *Size* | : |
| | • *Approximate number* | : |
| | • *Gross appearance:* | : involved/ Not involved |

**MICROSCOPY:**

| | | |
|---|---|---|
| | **Histological type** *(WHO Classification)* | : |
| | **Histological grade** | : |
| | **Extent of invasion** | : |
| | **Margins** *(check all that apply)* | |
| | – **Vaginal cuff** (tumor extension) | : Cannot be assessed/ uninvolved / involved |
| | | : Distance from resection margin ........ |
| | | : *In-situ* changes at margin present / absent |
| | – **Parametrium**(tumor extension) | : Cannot be assessed/ uninvolved / involved |
| | | : Distance from resection margin ........ |
| | | : *In-situ* changes at margin present / absent |
| | **LVSI** *(Lympho-Vascular Space Invasion)* | : Present / Absent/ indeterminate |
| | **Additional pathological findings** | : None/ Intraepithelial neoplasia/ Others |
| | **Endometrium** | : |
| | **Myometrium** | : |
| | **B/L Fallopian tubes & Ovaries** | : |
| | Lymph nodes | : Involved / Not involved |

| | Site / size | : |
| Perinodal spread | : Yes / No |
| Immunohistochemistry | : Not done / Done |
| If done, specify | : ............................... |

..........................

Comments: .................................................................................................

DIAGNOSIS                    :

<div align="right">Pathologist.</div>

## Appendix - C

## PRINCIPLES OF SURGERY

Stage IA1 patients are usually diagnosed after histological examination of the conization specimen. For these patients with stage IA1 disease, extrafascial (Piver class I) hysterectomy is recommended[55]. However, if the conization specimen shows presence of lymphovascular emboli, Piver class II radical hysterectomy is preferred. For patients desiring fertility preservation, radical trachelectomy with pelvic lymphadenectomy is an option. In patients with compromised performance status or severe co-mobidities, surveillance may be advised if the margins of the cone are free of tumour [56,57.]

Stage IA2-IIA:

The surgery that is recommended is radical hysterectomy (Piver Class III) with pelvic lymphadenectomy (Piver Classification)[55]. The aim of surgery is to remove the cervical disease with a wide tumour free margin that includes a wide parametrial and paracervical excision and a wide vaginal cuff. Surgery results in survival rates of 70-90% at 5 years [58] and identifies high risk patients needing adjuvant therapy.

Surgery may be carried out by the abdominal, vaginal or laparoscopic approach with equally good outcomes.

In selected patients with small tumours (IA2-IB1), where the risk of parametrial involvement is low [59-60], a modified radical hysterectomy (Piver class II) with adjuvant radiation therapy for high risk patients has been shown not to compromise survival and reduce the treatment related morbidity especially the bladder related and sexual morbidity [61-63].

The other option for these patients with small volume tumours, elective nerve sparing radical hysterectomy wherein the hypogastric nerves and the pelvic splanchnic plexus are identified and separated before resection of the parametrial tissue, may be carried out [64]. Although there are no randomized trials of nerve sparing versus standard radical hysterectomy class III, numerous authors have demonstrated oncological equal efficacy, safety and reduced morbidity with this procedure [65].

In young premenopausal women, bilateral ovarian preservation may be done with transposition of the ovaries in the paracolic gutters, as the rate of ovarian metastasis is very low [66,67].

In young women with cervical cancer, who are desirous of child bearing, in a select group of patients with tumour size <2 cm, radical trachelectomy with pelvic lymphadenectomy may be done. This may be done by the vaginal, abdominal or laparoscopic approach. Oncological safety and good fertility preservation & pregnancy rates have been reported, although the risk of abortions and premature delivery are higher [68-71]. The relapse rate in well selected patients is low and the survival figures are equivalent to those of radical hysterectomy [72].

A complete pelvic lymphadenectomy from the level where the ureter crosses the bifurcation of common iliac artery is recommended. Sentinel node sampling is under investigation for its usefulness in cervical cancer surgery[73]. False negative rates of about 10% have been reported using a combined blue dye and lympho-scintigraphy technique and the negative predictive value of the procedure is not sufficient to warrant its routine use to replace standard lymphadenectomy at present[74]. In the absence of sufficient validation data, this remains an area of research.

Stage IB2 patients may be treated with radical hysterectomy Piver class III with pelvic lymphadenectomy with or without para-aortic lymph node sampling. Pelvic lymph node dissection may be done first and if

negative, radical hysterectomy may be done. If the nodes are positive, then the hysterectomy should be abandoned and these patients should receive chemo-radiation.

**Minimal access surgery:** The role of minimal access surgery in management of cervical cancer is presently investigational. 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. 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 centers with large volume gynecologic oncological work. Initial results showed safety and feasibility of Robotic radical hysterectomy. However data on long term oncological outcome is lacking. Advantages of Minimal access surgery include less intra-operative blood loss, early post-operative recovery, shorter hospital stay and better cosmesis.

# PRINCIPLES OF RADIATION THERAPY

## Radical Radiation Therapy

## Conventional External Radiation Techniques:

*Radiation Planning*: Conventional planning is fluoroscopy guided with patient in supine position. Under fluoroscopy guidance, bony landmarks are used to mark the portals. The whole pelvis treatment fields typically extends from the L4-5 or L5-S1interspace superiorly to the mid-pubis or to a line 2 cm below the lowest vaginal disease. Radio-opaque markers may be placed in the vaginal cavity to identify the disease at cervix or vagina. The fields may be extended superiorly if the para-aortic nodes are to be treated prophylactically (high risk) or known to be involved. Lateral borders are placed at least 1.5 cms lateral to the bony pelvic brim. The lateral margins and shielding should be more generous if massive obesity reduces the reproducibility of the treatment setup.

In four field technique (antero-posterior and bilateral portals), the anterior border of the field usually includes the pubis to adequately cover the tumor with margins, the posterior border at S3 vertebra to include presacral nodes and uterosacral ligaments. Customized blocks to shield small bowel region anterio-superiorly and, low ano-rectum on the lateral fields in special situations. Additionally, inguinal nodes should be included if the disease is extending into/ beyond lower third of the vagina.

Using conventional fractionation, a dose of 40-50 Gy in 20-25 fractions over a period of 4-5 weeks is recommended. Use of two filed or four-field beam arrangement, corner shields and a special midline block (after 20 Gy), helps in reducing the dose to rectum, bladder and small bowel during external radiation.

*IntracavitaryBrachytherapy*: Brachytherapy plays a very important role in obtaining high cure rates with minimum complications. A good intracavitary insertion delivers a very high radiation dose to the cervix, upper vagina and medial parametria without exceeding the tolerance doses for rectum and bladder. The randomized trials comparing low dose rate (LDR) with high dose rate (HDR) brachytherapy in carcinoma cervix have shown that the two modalities are comparable in terms of local control and survival [75,76]. Thus, either LDR or HDR brachytherapy may be used, taking into account the availability of equipment and other logistics of treatment delivery. HDR brachytherapy can be done as a day procedure in contrast to approximately 20 hours of continuous LDR treatment requiring overnight inpatient stay. However, due to radiobiological considerations, 3-5 applications of HDR are required in contrast to 1-2 applications of LDR (for stage I and II) to maintain low complication rates. HDR is being increasingly used now as the control rates are comparable and the toxicity is slightly less. ***Grade A recommendations***

***The task force committee strongly recommends that the use of low dose rate intracavitary brachytherapy may be gradually phased out.***

The recommended brachytherapy schedules are either LDR 1-2 fractions of 25 - 30 Gy to point A each 1 week apart, or HDR 3 - 5 fractions of 6 - 7.5 Gy to point A each once weekly. Other HDR fractionation schedules are still investigational.

A combination of external-beam pelvic irradiation covering the uterus, parametria and pelvic nodes and intracavitary irradiation primarily for the central disease is used. The aim is to deliver a dose equivalent of 80Gy to point A. The planned radical radiation /concomitant chemo-radiation should be completed within 8 weeks without significant treatment breaks. Prolonged overall treatment time result is poor outcome [77] ***(Grade C recommendations)***

**Radiation therapy doses:**

**Stage IB-IIB:** Using conventional fractionation, an external radiation dose of 40-45 Gy in 20-25 fractions over a period of 4-5 weeks is recommended interspersed with brachytherapy applications of 1-2fractions of LDR or 3-5 fractions of HDR applications once weekly.

**Stage IIIA:** The dose of external beam radiation therapy is 50Gy to the whole pelvis over 5 weeks with 1.8 - 2 Gy fractionation. Whenever possible, a midline block should be used after 40Gy. The radiation portals are similar except that the inferior border is placed 2 cm beyond the lower vaginal disease or at introitus. An LDR Intracavitary application with tandem and ovoids to a dose of 30Gy to point A is recommended. Patients, in whom standard ICA is not feasible due to residual disease extending below upper third vagina, intracavitary application using tandem and cylinders to a dose of 15 - 25 Gy to point A (depending on rectal dose) is recommended.

**Stage IIIB:** The dose of external beam radiation therapy is 50 Gy to the whole pelvis over 5 weeks with 2 Gy fractionation. Whenever possible, a midline block should be used after 40 Gy. Intracavitary application with Low dose rate (one application of 30 Gy to point A) or High dose rate (3 applications of 7Gy to point A each every week, starting from 3rd or 4th week of external radiation) is recommended.

**Para-Aortic nodes:** Extended field radiation therapy has been reported to produce long term disease control in women with microscopic or small volume (<2cm) lower para-aortic nodes (below L3) with acceptable complications rates when radiation dose was not exceeded beyond 50 Gy and the lymphadenectomy was performed by extraperitoneal rather than transperitoneal route [78]. In the RTOG randomized trial reported recently, the 10 year overall survival was improved from 44% with pelvic radiation to 55% with pelvic plus prophylactic para-aortic radiation in 367 women with stage IB1 and IIA disease. Grade 4 and 5 radiation toxicities at 10 years however increased from 4% to 8% with para-aortic irradiation. Patients with positive common iliac or para aortic nodes may be treated by extended field radiation with or without chemotherapy [79,80,81]. *Grade C Recommendations.*

**Radiation therapy related side effects:** During pelvic radiotherapy, most patients experience mild fatigue and mild to moderate diarrhea that respond to anti-diarrheal medications and few may experience bladder irritation. These acute symptoms are increased when combine with concurrent chemotherapy or on extended fields. Patients receiving concurrent chemotherapy may additionally have hematological and nephro-toxicities especially with the use of cisplatin [82].

The late sequelae following radiation therapy commonly seen are rectal, bladder and small bowel. These depend on the duration of follow-up, type of treatment modalities and estimated radiation doses to these organs. The reported grade III/IV late sequelae (toxicities requiring hospital admission or Intervention) range from 5-15%.

Late Rectal Sequelae in the form of chronic tenesmus, telangiectasia and profuse bleeding, rectal ulceration and strictures have been reported (5-8%). These are usually seen during 18-36 months follow-up period. The treatment options include sucralfate enema, steroid enema, argon plasma coagulation (APC), laser therapy, or formalin applied to affected mucosa, diversion colostomy.

Late Bladder complications may occur in the form of continuous hematuria, necrosis and rarely vesico-vaginal or urethra-vaginal fistula. The incidence of symptomatic Grade III/IV late toxicities after radical radiation is 4-8%. HBOT therapy within 6 months of hematuria onset results in a good therapeutic response rate.

Late small bowel sequelae in the form of chronic enteritis, sub-acute intestinal obstruction, perforation, strictures etc. can be encountered. The incidence of symptomatic Grade III/IV late toxicities after radical radiation reported is 3-12%. These sequelae are higher in patients undergoing radical surgery esp. trans-peritoneal pelvic lymphadenectomies and adjuvant radiation +/- chemotherapy.

Most patients treated with radical radiotherapy have telangiectasia and fibrosis of the vagina, resulting in significant vaginal shortening especially in elderly, postmenopausal women and those with extensive tumors treated with a high dose of radiation. These to some extent can be prevented by counseling for regular sexual activity and vaginal dilatation exercises.

### Newer External Radiation Techniques:

In the past 10-15 years, there has been a rapid progress in radiation delivery techniques in parallel to advances in technology and imaging. Newer external radiation techniques like Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), PET-CT Guided Radiation etc. have also been explored in cervical cancers [83-87].

These techniques require thorough knowledge regarding CT or MRI anatomy, disease pathology and natural history. This helps to translate the understanding of conventional fields of 2D based on bony landmarks to 3D imaging like CT and MRI. Oncologist needs to contour (draw) the target volume and normal tissue so that radiation doses can be prescribed. The target in cervix cancer includes Gross tumour volume (GTV; which includes disease involving cervix and extensions when applicable to parametrium, vaginal wall, uterus, lymphnodes), Clinical target volume (CTV; includes whole of cervix, uterus, parametrium up to lateral pelvic wall and upper 2 cm of vagina below the lowermost gross involvement and lymphatics) and Planning target volume (PTV includes appropriate margins over CTV). Recently many authors have proposed guidelines to contour nodal/ lymphatic CTV in cervical cancer. Similar to identification of target volume, identification and contouring of normal tissue is vital because newer techniques like IMRT can achieve optimal sparing of normal tissues without compromising the doses to target. Various normal tissues contoured are bladder, rectum, sigmoid, small and large bowel and bone marrow [87,88].

There are potential advantages with use of IMRT over conventional 2D treatment. Most of these advantages have been described dosimetrically or have been used in small clinical series and need wider clinical testing and implementation with generation of supporting evidence. These advantages include:

- *Limiting doses to normal tissues:* This factor is of paramount importance and is going to be more and more relevant in coming days with increasing intensity of treatments used routinely. The conventional normal tissues include rectum, bladder, sigmoid and bowel; but this list is ever increasing. Bone marrow sparing IMRT is one of the recent concept that is evolving fast with clinical data. This is crucial development to be able to give safely high doses of RT to pelvis, concurrent and adjuvant aggressive chemotherapies and para-aortic radiation [87,88]

- *Dose escalation* to central tumor is theoretically important application of IMRT in any site. In cervical cancer brachytherapy excludes most of such need but still in locally advanced stages inappropriate geometry and size of residual disease after EBRT can lead to omission of brachytherapy. In such cases proper initial doses in EBRT are vital to get proper anatomy suitable for brachytherapy, also in cases where brachytherapy is still not feasible IMRT boost can be used to increase local control [83, 89].

- *Concomitant boost application* to special target regions can be achieved using IMRT. These regions may include pelvic or para-aortic lymphnodes or lateral one third of parametrium [79-81].

- *Prophylactic Extended field radiation* – with increasing stage risk of para-aortic lymphnodes involvement increases and would benefit with prophylactic treatment. Conventional treatments with 2D have been long criticized for increased bone marrow and bowel toxicity. But with IMRT the doses of 50 Gy can be safely delivered to these regions [79-81].

- *Radical treatments for para-aortic lymphnodes (PALN)* – Although FIGO staging does not change with identification of PALN identified in imaging alone but the treatment should. Recently several authors have tried giving radical doses of 60-66Gy with concurrent chemotherapy radically and demonstrated good local controls and acceptable toxicities [79-81].

## Recent advances in Cervical Brachytherapy:

Historically, there were systems like Manchester, Paris, Stockholm derived from rich clinical experience which was used to deliver specified dose to the tumor fairly accurately in the absence of treatment planning systems. Later with development of various manual and after-loaded applicators and different Radium substitutes like Cs-137, Co-60, Ir-192, potential of brachytherapy became evident. High Dose Rate (HDR) remote after-loading coupled with advances in treatment planning systems has ensured well defined protocols and methods for brachytherapy dose analysis. However, the imaging modality used in Brachytherapy was largely limited to 2D orthogonal radiographs. The major limitation of the conventional imaging modalities is applicator and point based and there is a lack of information on the tumor volumes and organs at risk (OAR). Conventionally, point doses are calculated for rectum and bladder according to ICRU-38 recommendations. But, point doses do not represent the dose received by the entire volume of the organs. Due to which the doses to the OAR's are not accurately known. Hence there is no significant correlation between the point doses and incidence of toxicities especially bladder. In addition, tumor cannot be seen in the radiographs, hence local control of the disease also is a challenge especially in larger tumors. In last 2 decades, significant technological advances have resulted in use of newer imaging modalities, planning algorithms and treatment delivery. This has resulted in use of imaging techniques for 3-D data acquisition, contouring for both target and various organs and optimizes treatment planning for brachytherapy applications.

Various imaging modalities like Ultrasound, CT, MRI and PET scans etc have been explored. Among all the imaging modalities, MR Imaging is becoming increasingly popular for diagnosis and treatment planning for EBRT and brachytherapy. Image Based Brachytherapy (IBBT) has been mainly possible due to MR imaging, where it is possible to image the applicator with tumor volume and other normal tissues. MR based IBBT is practiced mainly in Europe and few US centers, as compared to robust 2D outcome data, it is still evolving. GYN GEC-ESTRO network has published guidelines for the practice and reporting of image based brachytherapy, which has been widely accepted so that a unified approach is formed among the users of Image Based Brachytherapy [90,91]. These recommendations describe a gross tumour volume, which encompasses T2 bright areas in the cervix; the high-risk clinical target volume (HR-CTV), which encompasses the entire cervix and all visible or palpable disease at the time of brachytherapy; and the intermediate-risk (IR-CTV), which is a 1 cm margin around this high-risk CTV plus the initial sites of involvement. The intermediate-risk CTV includes vaginal extension at the time of diagnosis that may have significantly decreased over time, and requires subtracting the normal tissues. The group also recommends starting with the standard method of dose prescription, either point A or the 60 Gy reference volume, and then adjusting the loading pattern and dwell times to ensure comprehensive target coverage. All patients should have the D90, D100, and V100 recorded for the high-risk CTV[91]. At this time, treatment of the full length of the tandem with some modification of only the top dwell position based on sigmoid dosage is recommended. One of the largest series published so far is from Vienna group, who have reported

the clinical outcome of 156 patients treated with image guided adaptive brachytherapy combined with 3D conformal external beam radiotherapy (EBRT)±chemotherapy [92]. The results are promising with excellent local control rates of 95-100% at 3 years in limited/ favourable (IB/IIB) and 85-90% in large/ poor response (IIB/III/IV) groups with an acceptable treatment related morbidity rates. Compared to their historical series there is relative reduction in pelvic recurrence by 65-70% and reduction in major morbidity. Other outcome data published from Paris and Mumbai endorse the same[93]. This is being tested further in an ongoing multicentric study involving several institutes in Europe, US, and Asia.

The potential of Ultrasonography (US) as an alternate imaging modality for guidance of intracavitary brachytherapy in cervical cancer is also being explored now [94,95]. The advantages of universal availability of US, its cost effectiveness, advances in 3D & real time US imaging and small learning curve may be a potential area for clinical research especially in developing countries. Similarly CT has also been compared with MRI in few small dosimetric studies and need validation in larger clinical studies [96–98].

## Radiotherapy with Concurrent Cisplatin Chemotherapy

Five randomized phase III trials of radical RT alone versus concurrent cisplatin-based chemotherapy and RT, and meta-analyses subsequently have shown an absolute benefit in overall survival and progression free survival with concomitant chemo-radiotherapy in patients with stage IB2 to IVA disease as well as high risk patients after hysterectomy [99 - 106].

While chemo-radiotherapy is perhaps the new standard of care, it is worth remembering that these results were obtained in a trial setting, in women from affluent countries who had better nutritional or performance status and renal parameters as compared to the majority of our patients from lower socioeconomic status and advanced disease. Therefore in women with medical or social reasons for doubtful compliance or tolerance to combined modality treatment, radical radiotherapy alone without compromising the doses and duration can still be considered as the gold standard treatment approach in our setting.

## Management of patients who relapse after primary treatment:

Treatment decisions should be based on the performance status of the patient, the site of recurrence and/ or metastases, the extent of metastatic disease and the prior treatment.

## Therapeutic options for local relapse after Primary Surgery

Relapse in the pelvis following primary surgery may be treated by either radical radiation or in selected patients pelvic exenteration. Radical irradiation (+/-with or without concurrent chemotherapy) may cure a substantial proportion of those with isolated pelvic failure after primary surgery. Radiation dose and volume should be tailored to the extent of disease. Fifty Gray in 25# @ 1.8 Gy per day should be delivered to microscopic disease and using field reductions 64 to 66 Gy should be delivered to the gross tumour volume.

Pelvic Exenteration may be an alternative (particularly if a fistula is present) to radical radiotherapy and concurrent chemotherapy in selected patients without pelvic sidewall involvement.

**Local Recurrence after Primary Radiotherapy:** Selected patients with resectable recurrences should be considered for pelvic exenteration. The only potentially curative treatment after primary irradiation is pelvic exenteration. Patients should be selected carefully; those with resectable central recurrences that involve the bladder and/or rectum without evidence of intraperitoneal or extra pelvic spread and who have a dissectabletumour-free space along the pelvic sidewall are potentially suitable. The triad of unilateral leg edema, sciatic pain and ureteral obstruction almost always indicates unresectable disease

on the pelvic sidewall, and palliative measures are indicated. This surgery should be undertaken only in centres with facilities and expertise for this surgery available and only by teams who have the experience and commitment to look after the long-term rehabilitation of these patients. The prognosis is better for patients with a disease-free interval greater than six months, a recurrence 3 cm or less in diameter, and no sidewall fixation. The five-year survival for patients selected for treatment with pelvic exenteration is in the order of 30 – 60% and the operative mortality should be < 10%. In carefully selected patients, a radical hysterectomy may be performed. Suitable patients are mainly those whose central tumour is not more than 2 cm in diameter. *Grade C Recommendations.*

Since the institutions are different phases of development and infrastructure available. It is envisaged that they will improve over the period of time.

|  | Minimum | Optimal |
|---|---|---|
| External RT |  |  |
| Technique | Conventional | Conformal |
| Machine | Cobalt / low energy Linac | Linac with MLC's |
|  |  |  |
| Brachytherapy |  |  |
| LDR / HDR | TPS planning atleast once with orthogonal X-rays / Images | TPS planning for all Intracavitary applications |

## Appendix - E

## PRINCIPLES OF CHEMOTHERAPY

### INTRODUCTION:

Chemotherapy is the use of drugs to kill cancerous cells, which can be administered either intravenously, orally or locally at the tumour site. In haematological malignancies chemotherapy solely and in solid tumours chemotherapy in combination with surgery or radiotherapy has rendered many cancers curable. The practice of medical oncology primarily deals with the appropriate use of chemotherapy drugs and its success depends upon using the right drugs at sufficient doses so as to derive a good response with minimum toxicity.

### TYPES OF CHEMOTHERAPY:

Induction: High-dose, usually combination, chemotherapy given with the intent of inducing complete remission when initiating a curative regimen. The term is usually applied to hematologic malignancies but is equally applicable to solid tumors.

Consolidation: Repetition of the induction regimen in a patient who has achieved a complete remission after induction, with the intent of increasing cure rate or prolonging remission.

Intensification: Chemotherapy after complete remission with higher doses of the same agents used for induction or with different agents at high doses with the intent of increasing cure rate or remission duration.

Maintenance: Long-term, low-dose, single or combination chemotherapy in a patient who has achieved a complete remission, with the intent of delaying the regrowth of residual tumor cells.

Adjuvant: A short course of high-dose, usually combination chemotherapy in a patient with no evidence of residual cancer after surgery or radiotherapy, given with the intent of destroying a low number of residual tumor cells. Adjuvant chemotherapy has shown to improve the overall survival in cancer patients [107] and prevents recurrence of chemo-sensitive tumours [108].

Neoadjuvant: Adjuvant chemotherapy given in the preoperative or perioperative period. It helps in reducing the size of the primary tumour. Another rationale is that if chemotherapy is administered prior to surgery, the reaction at the primary tumor site may be a predictive marker of micrometastatic systemic disease response [109]. Based upon the response in the primary tumour we also can predict the nature of the disease and identify patients who may require aggressive therapy in the future [110].

Palliative: Chemotherapy given to control symptoms or prolong life in a patient in whom cure is unlikely.

Salvage: A potentially curative, high-dose, usually combination, regimen given in a patient who has failed or recurred following a different curative regimen.

**COMBINATION CHEMOTHERAPY**: It is the use of combination of two or more drugs from different classes used to treat a malignant disease e.g. the use of paclitaxel and carboplatin in ovarian malignancy. The rationale for combination chemotherapy is to minimise toxicity due to high dose of a single drug, synergistic effect of the combination drugs and thus greater anti neoplastic effect and to minimise drug resistance due to tumour cell heterogeneity as the disease progresses due to DNA instability and mutations [111].
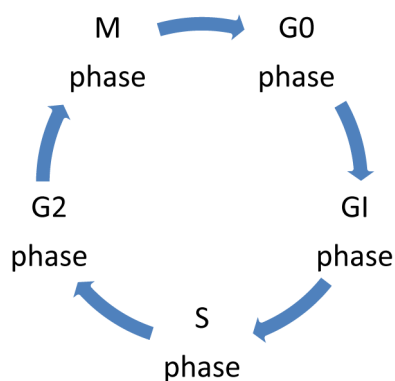
## CELL CYCLE:

In human body there are mainly three types of cells [112]:

1. Actively dividing cells
2. Terminally differentiated cells which can no longer divided
3. Resting cells, but which have potential to divide

The cell cycle has 5 phases:

1. G0 phase: In this phase the cells are in resting state.
2. G1: This is the phase, where the cells prepare for DNA synthesis
3. S phase: DNA synthesis takes place, to form tetraploid forms
4. G2 phase: This is the phase where cells prepare for mitosis and repair of the defective genetic material takes place
5. M phase: this is the active mitotic phase where two daughter cells are formed



The basic understanding of this cell cycle is important because chemotheraputic drugs can be classified broadly into two categories:

A. Cell-cycle phase specific: eg G0 phase specific- e.g. corticosteroids

G1 phase specific- e.g. asparaginase

S phase specific- e.g. 5fluorouracil, methotrexate

G2 phase specific- e.g. bleomycin, irinotecan

M phase specific- e.g. vinca alkaloids, taxanes

These drugs act only if the cells are in that specific phase of cell cycle. Hence above a certain dose further increase in the drug level will not enhance cell kill, but if the same concentration is maintained over a longer time then more cells can enter into that particular phase.

B. Cell-cycle phase non specific: e.g. alkylating agents

These drugs have a linear dose response curve; more the concentration more is the cell kill

**TUMOR CELL KINETICS**: Tumour growth depends on the fraction of cells dividing actively, tumour doubling time and the host immune system and destruction of tumour cells by apoptosis or necrosis.

When there is an increased fraction of actively dividing cells the tumour rapidly increases in size and after it has reached a particular size the growth ceases due to decrease in blood supply and hypoxia. A tumour becomes detectable when there are $10^9$ cells or 1 gram of tissue and $10^{12}$ cells leads to death.
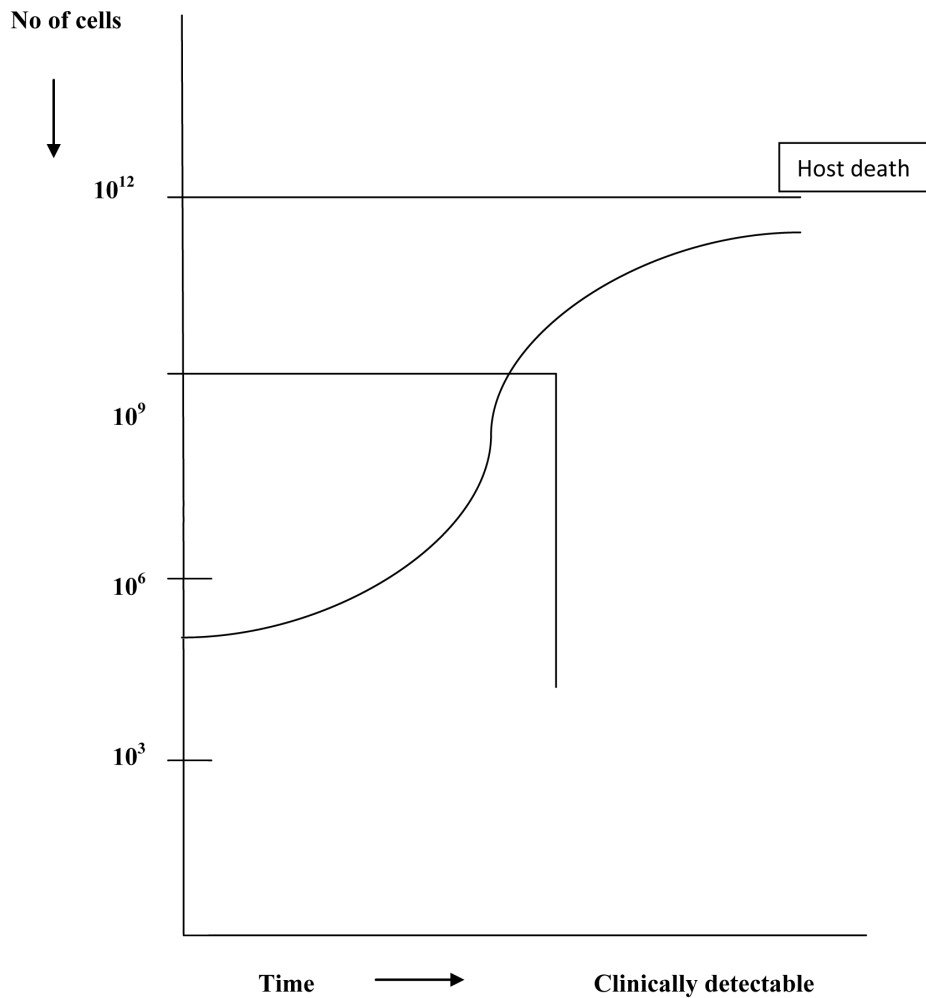


Tumour growth is best depicted by the Gompertzian model which suggests that uncontrolled growth eventually leads to a plateau phase of slow growth and eventually the tumour maintains a stable size. This important fact is important as most of the chemotherapy drugs act effectively at the fast dividing fraction as proposed in the Norton and Simon hypothesis that cell kill is proportional to the growth fraction. Hence smaller size tumours are more chemosensitive than larger size tumours.
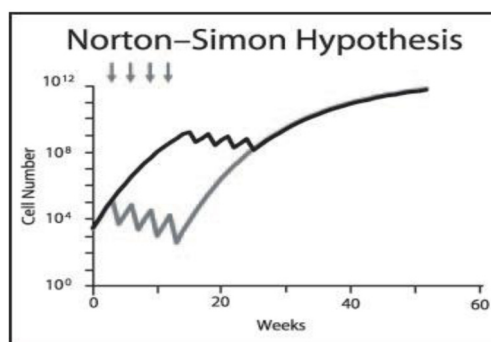
**MAJOR CLASSES OF ANTI NEOPLASTIC DRUGS:** Anti cancer drugs are divided into the following classes

| CLASS | EXAMPLE | MECHANISM OF ACTION | IMPORTANT TOXICITY |
|---|---|---|---|
| Alkylating agents | Busalfan Cyclophosphamide Cisplatin | Cross linking of DNA strands | Lung fibrosis Haemorrhagic Cystitis Neurotoxicity, Nephrotoxicity myelosuppression |
| Antimetabolites | 5 fluorouracil Methotrexate | Interferes with DNA synthesis by blocking necessary enzymes | Diarrhea Myellosuppression |
| Antitumour Antibiotics | Bleomycin Actinomycin D Doxorubicin | Intercalates with DNA and prevents its replication and Messenger RNA Production | Pneumonitis Hypersensitivity Myelosuppression cardiomyopathy |
| Mitotic spindle Agents | Paclitaxel dosetaxel Vincristine Vinblastine | Bind microtubular Proteins and Disrupt the mitotic Spindle | Neuropathy Hypersensitivity Neuropathy myelosuppression |
| Topoisomerase Inhibitors | Etoposide irinotecan | Inhibits topoisomer-Se which is essential To repair DNA Strand breaks | Myelosuppression diarrhea |
| Tyrosine kinase Inhibitors (TKI) | Imatinib Erlotinib Lapatinib | BCR-ABL TKI EGFR TKI EGFR & Her 2 TKI | Myelosuppression Acneiform rash diarrhea |
| Monockonal Antibodies | Rituximab Bevacizumab | Anti CD 20 ANTI VEGF | Infusion related Cytokine release |
| Hormonal agents | Tamoxifen Anastrazole | Anti estrogen Aromatase inhibitor | Hot flushes, vaginal Bleeding osteopenia |

**DRUG RESISTANCE:** Failure of chemotherapy has been a great concern and has led to discovery of more and more new drugs to treat cancer. Drug resistance can be inherited or acquired [114]. Acquired resistance is of more concern; as such tumours may be cross resistant to chemotherapy drugs of other classes in addition. The main causes of drug resistance are [115]:

1. increased drug efflux due to a protein called p glycoprotein encoded by multi drug resistance (MDR)1 gene

2. drug inactivation

3. alterations in drug target

4. repair of drug-induced damage, and evasion of apoptosis

5. mutations and development of resistant clones of cancer cells

**RESPONSE FOR CHEMOTHERAPY:** Objective response of the tumour to chemotherapy and overall survival are two important predictors of the efficacy of any chemotherapy regimen. Hence to have a fair

and objective response assessment RECIST (Response evaluation criteria in solid tumours) has been formulated, which specifically helps in a clinical trial setting. The important definitions under RECIST are as follows [116]:

- Complete Response (CR): Disappearance of all target lesions.

- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The appearance of one or more new lesions is also considered progression.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

The clinical application of RECIST by the help of imaging helps in making treatment decisions regarding continuation of the existing chemotherapy regimen or changing into next line of chemotherapy. However, patient's symptomatic improvement and quality of life are also important factors for such decisions.

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| 5-FU | 5-Fluorouracil |
|------|----------------|
| AIDS | Acquired Immune Deficiency Syndrome |
| APC | Argon Plasma Coagulation |
| ARV | Antiretroviral Therapy |
| ATZ | Abnormal Transformation Zone |
| CGIN | Cervical Glandular Intraepithelial Neoplasia |
| CIN | Carcinoma *in-situ* |
| CT | Chemotherapy |
| CT Scan | Computed Tomography Scan |
| CTV | Clinical Target Volume |
| DNA | Deoxyribonucleic acid |
| EBRT | External Beam Radiation Therapy |
| EP | Etoposide and *cis*Platinum chemotherapy |
| FOGO | International Federation of Gynecology and Obstetrics |
| GEC-ESTRO | *Groupe Europeen de Curietherapie*–European Society for Therapeutic Radiology and Oncology |
| GTV | Gross Tumor Volume |
| Gy | Gray |
| GYN | Gynecology |
| HBOT | Hyperbaric Oxygen Therapy |
| HDR | High Dose Rate |
| HPV | Human Papilloma Virus |
| HR-CTV | High Risk Clinical Target Volume |
| IBBT | Image Based Brachytherapy |
| ICA | Intracavitary Application |
| ICRU | International Commission on Radiation Units and Measurements |
| IGRT | Image Guided Radiation Therapy |
| IMRT | Intensity Modulated Radiation Therapy |
| IR-CTV | Intermediate Risk Clinical Target Volume |
| LDR | Low Dose Rate |
| LEEP | Loop Electrosurgical Excision Procedure |
| LVSI | Lympho-Vascular Space Involvement |
| MDR | Multi Drug Resistance |
| MLC | Multileaf Collimator |

| | |
|---|---|
| MRI | Magnetic Resonance Imaging |
| NCC | Neuroendocrine cancers of Cervix |
| NTZ | Normal Transformation Zone |
| OAR | Organs at risk |
| OS | Overall survival |
| PALN | Para-Aortic Lymph Node |
| Pap test | Papanicolaou test |
| PCR | Polymerase Chain Reaction |
| PET-CT | Positron Emission Tomography-Computerised Tomography |
| PFS | Progression Free Survival |
| PLND | Pelvic Lymph Node Dissection |
| PTV | Planning Target Volume |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RH | Radical Hysterectomy |
| RNA | Ribonucleic acid |
| RR | Relapse Rate |
| RT | Radiation Therapy |
| RTOG | Radiation Therapy Oncology Group |
| SCCC | Small Cell Carcinoma of Cervix |
| SIADH | Syndrome of Inappropriate Antidiuretic Hormone |
| TPS | Treatment Planning System |
| US | Ultrasonography |
| VAC | Vincristine, Dactinomycin, Cyclophophamide |
| WHO | World Health Organisation |
| Wks | Weeks |