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Comprehensive Review Of Cervical Cancer Management: Current Treatment Strategies And Future Prospects

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Abstract: The fourth most common illness among women worldwide is cervical cancer, continuous to be a serious global health problem. An ongoing infection with high-risk HPV genotype, especially HPV-16, and HPV-18, is the main cause of it. Cervical cancer has been shown to be less common be early screening and immunization program; the world health organization has published a strategic plan to end Cervical cancer worldwide by 2030. This cover high performance screening HPV vaccination, and promote treatment of precancerous lesion. A multidisciplinary approach is being used to treat Cervical cancer, and treatments include surgery, radiation therapy, Chemotherapy and newly developed targeted immunotherapy therapies. Modern screening methods, such HPV DNA testing, have more sensitivity than conventional cytology and can identify high grade lesions early. Treatment plan that are customized based on patient characteristics like fertility preservation and the disease stage of cervical cancer are guided by the staging and categorization for the illness, mostly as per the FIGO and TNM system. Depending on the level of invasion and reproductive concern, surgical treatment for early-stage illness varies from cone biopsies to more drastic operation including trachelectomy and hysterectomy. In resource rich areas, chemotherapy is still the standard treatment for locally advanced cervical cancer; however, for advanced or metastatic illness, immunotherapy and other palliative measures show promise. Moreover, increasing studies in molecular therapeutic, offer adoptive T cell treatment and the administration of checkpoint inhibiting drugs, are opening new possibilities in cervical cancer treatment. Cervical cancer management remains challenging despite these developments due to inequality in access to healthcare, especially in low resource settings. Resources appropriate strategies including self-sampling HPV testing, visual inspection method, and inexpensive therapies likes cryotherapy are being used to close this disparity. In order to enhance outcome for women worldwide, this study examines the full management of cervical cancer, emphasizing existing medicines, preventive measures, and the future direction of individualized treatment.

Keywords **-** Cervical cancer, Genotype, Chemotherapy, Immunotherapy, Molecular therapeutic

I. INTRODUCTION

Cervical cancer is the fourth most Lethal malignancy worldwide for women. With a frequency of 123907 new cases identified and 77348 deaths annually [1]. Human Papillomavirus (HPV), a sexually transmitted virus with over 200 genotypes, is the main driver of cervical carcinogenesis. Among of these enduring infection with high-risk category like HPV-16 accounting 50%, and HPV-18 accounting 10% pose the highest risk of developing invasive cancer and cervical precancerous lesions [2]. When a person has one of these two HPV strains, their risk of acquiring cancer risk 435 times and 248 times, respectively, above that of an uninfected person [3]. Other risk factors include age at which a person had their first sexual experience, several partners, Equitable, co-infection from smoking, long term oral contraceptive usage, dysphagia of the cervical canal [3]. The squamous epithelium's basal cell, which are where keratinocytes develop, are infected by HPV. When the viral and host DNA combine, a fraction of HPV infection culminates in malignant transformation. These genes are necessary for the control of the cell cycle and apoptosis, therefore if they are suppressed, cancer may result. Persistence HPV infection is encouraged by immunosuppression. At the molecular level, HPV co-infection can also encourage HPV related malignant transformation. Hormone replacement treatment (HRT) and oral contraceptive have the potential to increase HPV expression. Active lifestyle choices are another risk factor that malignant contribute to persistence HPV infection [4]. Typically, Cervical cancer develops from Cervical intraepithelial neoplasia (CIN). Whereas not all cases of CIN develop to cancer (and most autonomously regress), this happens over a period of 10-20 years. When the epithelium's basement membrane is broken, invasive cervical cancer develops [5]. The WHO director-General released the international strategy for faster the elimination of cervical cancer in November 2020. The strategy includes the following for each of the three pillars for 2030: 90% of suitable girls will be vaccinated against HPV, 70% of girls will have high performance testing done, and 90% of women will either receive appropriate treatment for a cervical lesion or a positive screening result.[6].

II. Screening and early detection

The Indian National cancer control program (NCCP) aims to prevent cervical cancer by promoting early identification and treatment. [7]. The difference in cervical cancer incidence between high and low occurrence nations can be attributed to effective mass screening programs. Testing for ongoing HPV DNA or performing pap smear cytology are two methods for screening. Due to the fact that it detects the virus in neighboring uncommon squamous cells of uncertain significance (ASCUS) and aberrant cells, latter test is more sensitive. Within the lesion, normal appearing cells also include latent papilloma virus DNA. For these reasons, the majority of studies have found that the HPV DNA test has a much higher cross-sectional sensitivity than cytology in identifying CIN 2 and 3 invasive carcinomas. Colposcopically guided biopsies are the gold standard for diagnosing cervical cancer because they show the precise arrangements of aberrant cells that were left behind after scraping. Crucially, most women who have cervical cancer are unable to produce an immune response to remove the virus infected cells from their cervix and have not a screening for last five years. Generally speaking, abnormal pap smears or DNA tests that are positive for carcinogenic HPV, particularly HP 16, after two consecutive positive screening tests indicate that the woman is more likely to

develop a high-grade lesion [8]. Randomized study conducted in high and middle income nation have shown that HPV testing is more sensitive than cytology and can prevent a higher number of cervical cancer [9] Other four visual inspection based methods for the early identification of cervical neoplasia are following: a) Unaided visual inspection (UVI), sometime referred to as "downstaging" is the practice of seeing the cervix with the naked eye without the use of acetic acid by medical professional; b) visual evaluation of the cervix with unaided eyes after applying 3-5% acetic acid (VIA); c) visual examination of the cervix using magnifying glasses(VIAM); d) visual examination after using ugol's iodine (VILI).[10].

III. Staging of cervical cancer

Table 1: classification of FIGO staging, TNM: cervical carcinoma

T category	Stages	FIGO definition	Feature of the patient	Option to consider	Remark or possible issues
TX		Primary tumor cannot be assessed.			
T0	Stage 0	The cervix's inner lining contains aberrant cells. These aberrant cells might develop into cancer and spread to neighboring healthy tissue. The term Carcinoma in situ refer to stage 0	The diagnosis of visible lesions must be confirmed by Biopsy. Blood count, such as a whole blood count, liver, kidney and HIV/syphilis serology may be taken into.	For staging, the following methods are acceptable: Pulse, examination, colposcopy, endocervical curetting, ultrasound, laparoscopy, proctoscopy, intravenous pyelography, and x-ray evaluation of the lung and bone are suitable	MRI, CT scan is potentially possible.

				techniques for staging.	
T1	Stage I	Cervical cancer restricted to the cervix, ignore any spread to the corpus.	Gross lesion not visible	Using a cervical cone biopsy to measure the breadth and depth	In cases when fertility is sought, congenital anomalies and radical trachelectomy may raise the risk of preterm. Hysterectomy or modified radical hysterectomy is thought to be the last treatment option when childbearing is finished
T1a	Stage IA1	Invasive cancer, only detectable by microscopy, limited to the cervix. The invasion of the stroma is about 3mm deep and 7mm wide	A1: desires fertility	A1: cone with well monitored results and negative margins	
			A1: reproduction is unimportant	A1: hysterectomy	
T1a2	Stage IA2	Cervical invasive cancer that can only be identified by the microscopy. The invasion of the stroma is approximately 3mm deep, 5mm wide, and 7mm horizontally dispersed	A2: desires fertility	A2: big cone with poor margins or trachelectomy that is radical and include node assessment	
			A2: fertility not a factor	A2: modified radical hysterectomy with dissection of the nodes.	
T1b	Stage I B	Clinically, cancer is limited to the cervical cavity, or there is preclinical lesion larger than A2	With professional guidance, less invasive (modified radical hysterectomy)		The incidence of ureteric fistulas is low and comparable foe two treatment modalities.

T1b1	StageIB1	Cervical invasive carcinoma with a maximum diameter is >4cm, either a microscopic lesion with ≥ IA2 classification or a clinically evident lesion.	treatment may be considered for tumors <2cm and with <50% cervical invasion	Chemotherapy in along with radiotherapy.	In premenopausal women, radiation induces ovarian failure
T1b2	StageIB2	Cervical invasive cancer with a clinically apparent lesion that is <4cm in diameter.		Radical hysterectomy combined with pelvic lymph nodes	
T2	Stage II	Beyond the uterus, cancer spreads but it does not reach the wall of the pelvis or the bottom portion of the vagina.	Under professional guidance, patient with II A malignancies that have just a little spread throughout the upper part of the vagina may be suitable for radical hysterectomy and pelvic lymph node dissection.	Treatment with radiation and concomitant chemotherapy is the main approach.	Short- and long-term radiation adverse effect in the bladder and colon
T2a	Stage II A	Tumor spread to the vaginal wall but not to the bottom portion of the vagina. Not a breach of parametrization.			
T2a1	Stage II A1	Clinically evident lesion that is smaller than 4cm in size and only affect			

		the top two third of the cervix.			
T2a2	Stage II A2	Clinically evident lesion that is smaller than the top two third of the cervix and has a maximum diameter of more than 4cm			
T2b	Stage II B	Tumor spread outside of the cervix. Invasion of the pelvic walls and the lower part of the vagina, but not of the parametrium.			
T3	Stage III	The tumor affects the lower section of the vagina, the pelvic wall, hydronephrosis, or nonfunctioning kidney, as well as the pelvic and/or para-aortic lymph nodes.	Unless there is proof that another cause is identified, all individual having hydronephrosis or dysfunctional kidney are classified as stage III	Treatment with radiation and concomitant chemotherapy is the main approach.	
T3a	Stage III A	Tumor confined to lower vaginal region; no expansion to the pelvic wall			

T3b	Stage III B	The tumor spread to the pelvic wall and may result in hydronephrosis or kidney failure			
T3c	Stage III C	The involvement of pelvic and/ or para- aortic lymph nodes occurs regardless of the tumor's size and spread.			
T4	Stage IV	Tumor spread beyond the actual pelvis and/or invade the bladder or rectum's mucosa, as demonstrated by biopsy	Based on the precise manner in which the illness has spread, these individuals need very customized care.	Depending on the specifics of each patient's condition, radiation and/or chemotherapy may be recommended.	Complementary or palliative treatment alone may be beneficial for patients with IV B (widely metastatic illness).
T4a	Stage IV A	The tumor has progressed to nearby pelvic organs.			
T4b [14]	Stage IV B [13]	Tumor has progressed to other organs.[3][12]			
	Recurrence the following first surgery		Decide after consulting with expert.	If localized, chemoradiation or radiotherapy could be useful.	

	Recurrence following initial radiation therapy.		Decide after consulting with expert.[11]	If localized, surgery or exonerative treatment could be useful.	

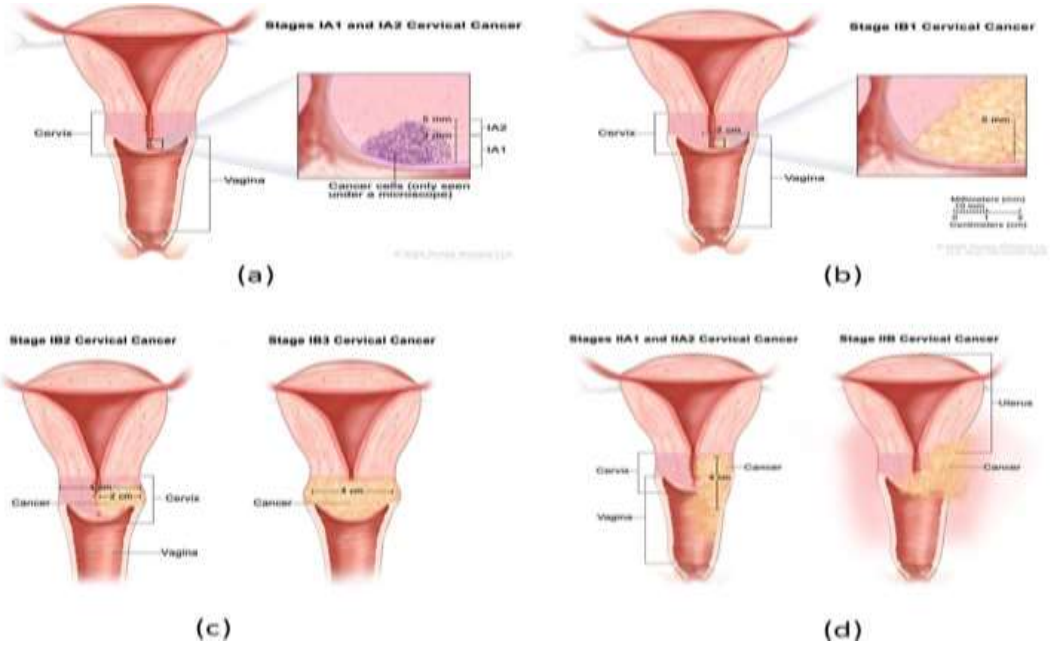

Figure 1. (a) stages IA1 and IA 2 cervical cancer, (b) stage IB 1 cervical cancer. (c) stages IB2 and IB3 cervical cancer, (d) stages IIA 1 and IIA 2 cervical cancer

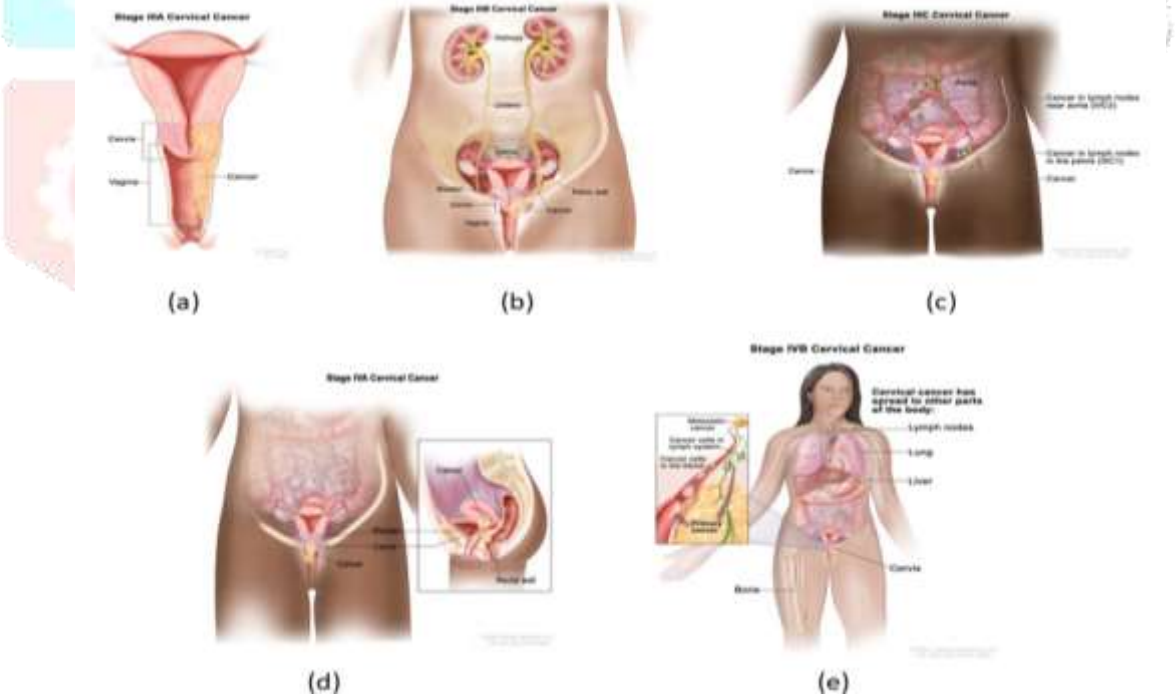

Figure 2[15]. (a) stage III A cervical cancer, (b) stage III B cervical cancer. (c) stage III C cervical cancer. (d) stage IV A cervical cancer. (e) stage IV B cervical cancer.

IV. Prevention:

Because to efficient screening, vaccination against the most carcinogenic strains of HPV and quality life prevention, cervical cancer is a condition which may be prevented and has a decreasing incidence. Completing the appropriate vaccine series and using public health technique to lower incidence are important preventive measure. According to reports, using condoms can prevent HPV transmission by about 70% [3].

- Additionally, healthy sex habits lower the chance of contracting HPV and other STDs. Generic warts are caused by HPV infection. It is best to stay away from having sex with HPV positive people.
- Regular pap screening can aid in the detection of pre-cancerous abnormalities so that can be treated before cervical cancer develops. Effectivity detecting such alterations. Pap smear needs to be performed on a frequent basis. Early year pelvic exam with pap smears should be conducted starting when a woman gets sexually engaged, or by the age of 20 for a woman who is not sexually active. In general, there was a lack of understanding and misunderstanding among many ethnic groups about the pap test, HPV and cervical cancer risk factor.
- Women who smoke regularly were advised to give up since smoking increases the risk of cervical cancer. In many nations, smoking is acknowledged as the primary cause of mortality from cancer. To being the process of altering one's behavior, one must first decide to quit [16].

Table 2. new methods being developed to prevent cervical cancer

Technology	**Synopsis**	**Utilization**
Heat induced ablation	To eradicate a cervical precancerous lesion, employ heat beams.	Substantial promise for preventing Cervical cancer.
Automated Liquid based cytology	This is compatible with automated analysis, improve case adequacy and lab efficiency, and make HPV testing easier.	Increased effectiveness of screening
HPV molecular test at the point of care.	Played a vital part in enabling the clinical research team to provide posttest counselling to women who had positive HPV testing.	Method for sampling oneself as well as high resolution micro endoscopy.
Molecular testing advancement	Using genomic method, oncogene and tumor suppressor gene profile are examined at the DNA level with an emphasis on biomarkers linked to HPV infection that are clinically significant	High risk HPV-DNA testing integrated into preventive initiative, with potential for enhanced risk assessments and triage.
Artificial cognition	AI help noninvasive cervical cancer distinction, improve interpretation efficiency accuracy, and facilities the triaging of HPV positive patients.	Real time diagnostic that is precise and quick, automated identification of cervical cancer and benign tumors.
Precision medicine	Modifying preventative and therapeutic approaches in light of	Personalized treatment and support using digital health intervention and genomic

	each patient unique genetic, environment, and lifestyle factors.	approaches for genotype-phenotype relationships.
CRISPR/Cas9 application	Used in molecular diagnostics, cancer susceptibility gene identification, treatment of cervical cancer tumors in mice and possible human trials involving PD-1 and HPV.	Capability as an adaptable tool for cervical cancer medical care and research.
RNA interference	Reduction in the amount of E6 and E7 mRNA , death in cancer cell types, and suppression of target gene	Promising as a cervical cancer treatment method via genetic engineering.
Biomarkers	mRNAs, proteins, p16INKa-67, HPV E6/E7 oncogene transcript, M-CSF, VEGF, DNA methylation, PD- L1 status are all related to HPV DNA testing.	Possibility of improving prognosis and early identification; further study is required for clinical applicability. [17]

V. HPV vaccination:

The development of nationwide immunization campaigns against high-risk HPV is one of the among the most significant recent developments in the fight against cervical cancer. Additionally, the HPV vaccination guard against infection that might result in penile, anal, vulvar, vaginal, and cancer of throat's recurrence (oropharyngeal cancer) [18]. Vaccination results in the creation of antibodies that attach to the HPV virus and prevent cervical infection. Currently there are three different kind of HPV vaccinations in use. A bivalent vaccination called Cervix guard against HPV stains 16 and 18, which are linked to cervical cancer. This vaccination, sometime known as Gardasil or Silgard, is quadrivalent. The nine-valent Gardasil 9 vaccination protect across HPV type 6, 11, 16, 18 as well as type 31, 33, 45, 52 and 58. A significant advancement in the battle against cervical cancer has been made possible by the release of Gardasil and Cervarix on to the market [4]. An intramuscular dose of 0.5ml of vaccine can be administered to the anterolateral thigh or deltoid muscle. It can be purchased as an injection ready sterile suspension in a prefilled syringe or a single dose vial; both need to be well shaken before use. It is important to adhere to manufacture recommendations for vaccination administration and storage. Starting vaccination is recommended for individuals aged 9 to 12, with catchup vaccination allowed until age 26. Three doses of Gardasil at 0,2, and 6 months are recommended; when using cervarix, there should be a minimum of 4 week's gap between the first and second doses, 12 week's gap between the doses and third doses, 24 week's gap between the first and third dose. It is possible to provide HPV vaccination alongside other vaccination like Tdap and Hepatitis B. It is not necessary to restarted the HPV vaccination series in the event that the timetable is the disrupted. Both doses need to be administered

promptly as practical. If the series stopped after the first dose, within the 12 weeks gap between the second and third doses. Give the third dosage right away as it is practical. There's just one that's running late [19]. Recently licensed vaccination aimed at avoiding cervical cancer: Cervix (vaccination against recombinant HPV Bivalent), Gardasil (vaccine against genetic HPV Quadrivalent),Gardasil 9 (Recombinant HPV nonavalent vaccines, Recombinant HPV Bivalent vaccine, Recombinant HPV nonvalent vaccine [20].

Pregnancy related contraindications, safety measures, and HPV vaccine usage: A history of severe allergic response caused by an HPV vaccine part or a serious allergic reaction that occurred after the HPV vaccines first dosage are contraindicated. Precautions: After receiving the HPV vaccination, patient should sit and monitored for at least 15min in order to avoid syncope and/or harm from fainting. Pregnant women should not receive vaccination if there are no well controlled studies on them. A pregnancy test is not receiving vaccination if there are no well controlled studies on them. Mistakenly obtaining a vaccination while pregnant shouldn't be consider stopping the pregnancy. If a woman becomes pregnant after receiving her first vaccine dose, any more doses that may be necessary should be delayed until after pregnancy [21].

VI. Quality of life:

Physical and psychological morbidities linked to cervical cancer have a detrimental effect on quality of life. African National routinely have higher rate of cancer related age-adjusted, daily-adjusted life years (DALY) lost than do high resource nations. Patient with radiotherapy treated inoperable cervical cancer have the lowest quality of life; most report a decline in social, emotional, physical, and financial support; they also have the highest chance of long-term bladder and bowel problems as well as psychosocial repercussions. Persistent bleeding from the vagina and persistent radiation enteritis are example of treatment- related side effect that might have a detrimental effect on a patient, both physical and social quality of life. There have been documented report in Kenya and south Africa of significant alteration in the sexual stage that led to disagreement in marriage and a decline in partner support throughout treatment and survival. Furthermore, given the culture and emotional significant of motherhood, young women may face substantial ramifications from the lack of the therapeutic alternative that maintain fertility. Before beginning treatment, patient with the cervical cancer who are with reproductive age should have an open discussion regarding issues linked to fertility and sexuality [22].

VII. Management:

In the present time, surgery, chemotherapy, and radiation are the main ways that Cervical cancer is treated in hospital. The general opinion holds that chemotherapy mediation have little effect on cervical cancer. As a result, the usual treatment options include radiation and surgery. But as a science progresses, a growing body of experimental data as well as clinical experience has demonstrated that the radiation and surgery alone cannot totally prevent or control the development and spread of cervical cancer. As chemotherapy medication have been replaced and drug delivery techniques have improved, drugs target therapy has progressively gained importance in the treatment of cervical cancer. Through various techniques, a number of gene mutations have been discovered in cervical cancer tissue recently. These alterations may include driving genes responsible for carcinogenesis and progression, making them potential targets for antitumor treatment [23]

A. Pre-invasive Lesions:

A very small portion of CIN can grow into an invasive tumor, and cervical cancer has significant pre invasive stage. Cervical cancer that invades the body can be avoided with the proper CIN care. While there isn't a clear-cut better surgical method for testing CIN, lower resources setting find interest in cryotherapy and loop electrosurgical excision process (LEEP). Given the prevalence of cervical cancer, an altering strategy that does away with cytology and colposcopy might be taken into consideration in an ultrashort resources' context [24]. In order to rule out micro invasive illnesses, surgical removal is recommended since it allows for further pathologic investigation. These people need lifetime monitoring following therapy [25].

Table: 3. resource-based approaches to the treatment of CIN and cervical cancer screening

	Good resource setting	**Limited resource setting**
Method of Screening	HPV investigation preliminary HPV detection Co-testing (cytology and HPV) Morphology VIA	Visual examination of the cervix using acetic acid or VIA Use an affordable self-sampling HPV test is feasible.
Triage tool	HPV test: cytology+ more recent modalities for ASCUS cytology High risk HPV test: Alternatively, VIA and biopsy++, colposcopy and biopsy++, colposcopy and biopsy++, or HPV genotyping for types 16 and 18.	If possible, Colposcopy Biopsy ++
Option for histopathological management that demonstrated CIN	LEEP can treat any case of CIN2 or CIN3. If AIS or early invasive cancer is suspected, CKC can be carried out. If CIN1 worsen or continue beyond two years, treatment options include follow up care and medication. If the requirements for ablation are met, thermal ablation or cryotherapy can be used as a substitute to LEEP for every level of CIN$.	Thermal ablation or cryotherapy should be used to treat any grade of CIN that meets the requirements for ablation $. All CIN grade that doesn't meets the requirements ought to be handled by LEEP. CKC can be done if early invasive cancer(AIS) is suspected.
Method to cut down on amount of visit.	When treating women who have a high-grade lesion that are suspected colposcopically, the	The "see and treat" approach ought to be employed, provided

	"sea and treat approach" is recommended. The treatment options ablative or LLETZ/ LEEP, depending on whether the lesion is suitable for ablative therapy. Reviewing the histopathology report is necessary during the follow up.	that colposcopy facilities are accessible. Females who exhibit positive HPV tests or who have VIA may be offered "screen and treat therapy", if colposcopy cannot be available. First, each case should be evaluated to see whether ablative treatment such as cryotherapy or thermal ablation is appropriate. After using 5% acetic acid, the eligibility of will female with positive HPV test results be evaluated (VIA). Before ablative therapy, a punch biopsy needs to be performed, and the results should be examined during the follow up. [26]

Key words: Cold knife colonization is known as CKS; loop excision of transformation zone/ loop electrosurgical excision method is known as LLETZ/LEEP.

+ More recent techniques

++ Biopsy from any abnormal areas

VIII. Requirement for removal:

The tumor has to meet specific requirements in order to be evaluated for cryotherapy. a) It must to be completely visible and limited to the cervix two areas; b) it must be entirely on the ecto cervix and not extend vaginally endo cervically; c) the biggest cryotherapy probe that is currently on the market must entirely cover it; d) there must be no indication of an invasive illness e) it cannot be performed in cases involving hemorrhage after menopause, a noticeable cervical growth, an uneven surface, or bleeding when touched.

B. Early cervical cancer (stage I A, I B1, I B2) :

In stage IA1 cervical carcinoma, the incidence of nodal metastasis is 1% when stromal invasion is less than 1mm, and 1.5% when it is between 1-3mm. The risk of cancer recurrence and lymph node metastasis in stage IA1 with LVSI are 5%. In stage IA2 with LVSI are 5%. In stage IA2 cancer, there is 7% chance of lymph node metastatic and the recurrence of the condition is 4% likely. [27]. Pelvic radiation therapy is currently a category 1 recommendation, per National Comprehensive Cancer Network (NCCN) guidelines, for women with high risk factor and negative lymph node following surgery in stage I A disease [25]. Cone biopsy (cold knife cone preferred over LVSI) can be used to treat IA1 with or without LVSI and 1A2. Ideally, the specimen should be non-fragmented with a 3mm negative margin [28]. In the event that the cone's margin is negative

the patient can be maintained under observation and monitored if necessary. If the patient is discovered to be non-operable, an operable extra fascial hysterectomy can be performed without the need for LVSI. If desired fertility and positive margins are found, a surgical cheilectomy with dissection of the pelvic lymph nodes should be performed. For a more comprehensive assessment at stage A1 without LVSI, paraaortic lymph node mapping, and/or LVSI, as well as IA2 or repeat cone biopsy, may be taken into consideration. When a patient is hopping in order to avoid

If conceiving is desired, radical trachelectomy and pelvic lymphadenopathy (laparoscopic are open) can be done in stage IA1 and IB1 with lesion less than 2cm in diameter. Young, low BMI individuals with tumor less than 2cm, no nodal involvement, and tumor not above the internal is on MRI had high cure rates and successfully pregnancies. The uterine body and it's attachment are removed during a radical trachelectomy, which also removes the cervix, vaginal margin and supporting ligament. The abdominal or vaginal routes might be used during procedure. Although parametrium excision via the abdominal approach can be accomplished more effectively, there will be less preservation of fertility. Radical trachelectomy is not recommended for neuroendocrine histology tumor or adenoma maligum because of their aggressive nature [27]. Adjuvant therapy and surgical findings in stage IB2 an IIA2- If the patient margin and parametrium are negative after surgery and her nodes are negative, she may be kept under observation or receive pelvic radiation therapy if her risk factors are present, either with or without concurrent cisplatin-based chemotherapy vaginal brachytherapy is an option if pelvic nodes, the surgical margin, the parametrium, and/or pelvic RT with CCCT are proven to be positive.

Table 4: combination the use of the fertility sparing technique with stage- specific guidelines for cervical cancer in its earliest stages

	NCCN Guidelines		**NCCN Framework for resource stratification**		**ASCO Resource Stratified clinical practice guidelines**	
Stage	Impairment of Fertility	Non fertility sparing	Fertility sparing	Non fertility sparing	Fertility sparing	Non fertility sparing
I A 1(no LVSI)	Cone biopsy	Simple hysterectomy	Cone biopsy	Simple hysterectomy	Cone biopsy	Cone biopsy or Simple hysterectomy
I A1+ LVSI, or I A2	Cone biopsy+ pelvic lymph node dissection	Modified radical hysterectomy+ pelvic lymph node dissection	Cone biopsy	Simple hysterectomy	Cone biopsy	Cone biopsy
	OR		OR		OR	
	Radical trachelectomy+ pelvic lymph node dissection	Pelvic RT+ brachytherapy	Cone biopsy	Modified radical hysterectomy	Cone biopsy	Simple hysterectomy

I B1	Radical trachelectomy+ pelvic lymph node dissection	Radical hysterectomy+ pelvic lymph node dissection	NA	Simple hysterectomy+ pelvic lymph node dissection	NA	Simple hysterectomy
		OR		OR		OR
		Pelvic RT+ brachytherapy		Modified radical hysterectomy+ pelvic lymph node dissection		NACT+ simple hysterectomy
II A1	NA	Radical hysterectomy+ pelvic lymph node dissection	NA	Simple hysterectomy+ pelvic lymph node dissection	NA	Simple hysterectomy
		OR		OR		OR
		Pelvic RT + brachytherapy		Modified radical hysterectomy+ pelvic lymph node dissection		NACT + Simple hysterectomy
I B2	NA	Definitive pelvic RT+ concurrent cisplatin containing chemotherapy+ brachytherapy	NA	Examination of pelvic lymph nodes and radical trachelectomy	NA	NACT+ simple hysterectomy
		OR		OR		OR
		Pelvic lymph node biopsy combined with radical hysterectomy (in the event that NACT is unavailable.				Simple hysterectomy (if NACT not available)
						Adjuvant chemotherapy after hysterectomy if histological

						risk factors present.[29]

C. Locally Advanced cervical cancer (Stages II B, III, IV A):

In a resource rich locale, simultaneous chemoradiation is the cornerstone of initial treatment for locally advanced cervica . The following explanation relates to squamous cell carcinoma, adenocarcinoma, and Adeosquamous carcinoma since these three kinds account for more than 90% of all cases of cervical cancer based on histology. For chemoradiation, individual with cervical cancer that has spread regionally may be candidates. Concurrent radiation therapy and 5 cycle of weekly cisplatin 40mg/m2 is followed by a sequential brachytherapy preferred course of treatment [30]. Primary chemoradiation may not be best option for stage llA1 illness; instead, surgical treatment with lymphadenectomy may be recommended. Surgery by itself is unlikely to be curative in stage IIB through IV A illness and surgery than primary chemoradiation. In ordinary practice, doublet treatment containing cisplatin administration concurrently with radiation are no longer recommended. For instance, concurrent radiation therapy with cisplatin and fluorouracil (FU) did not increase the complete response rate or progression-free survival (PES), 4-year survival over single agent cisplatin with radiation, although it did increase morbidity. Patient who do not meet the requirements for cisplatin, such as those with substantial baseline neuropathy or preexisting chronic renal failure, mat benefit from weekly carboplatin dose. Normalizing renal function may make patient eligible for cisplatin again if they have malignant ureteral obstruction related renal impairment. Therefore, ureteral stenting should be utilized to restore urine flow before beginning therapy. Few studies support the first line use of medicines other than carboplatin first line chemotherapy and radiotherapy. An encouraging investigation on the Gemcitabine as a single agent has highlighted the need for more research, and other studies using the drugs utilized in the case of recurrence, single agent paclitaxel and FU, have not demonstrated suitable benefits profile in primary therapy to support recommendations.

The standard of care of LACC includes brachytherapy as a means of elevating the dosage to the cervix uteri in a targeted manner, so addressing any possible residual illness. Along with being extremely beneficial for survival, it is linked to a reduction in severe toxicities and local relapse. More local control and fewer toxicities were further toxicities were further improved by the incorporation of 3D treatment planning brachytherapy based on MRI evaluation, which decreased dose in organ at risk and increased dosage to the tumor [30]. It is important for medical oncologist to be aware that the suggested treatment plan for LACC include boosting brachytherapy using external beam radiation treatment (EBRT). The most popular first treatment is pelvic EBRT, which should encompass all disease site. Extended field radiation to include the para aortic lymph node must be considered in patients with high common pelvic and para aortic nodal involvement. However, this approach carries a large morbidity cost. It is advised that all patients start brachytherapy at this time when the tumor has approximately decreased, which often happens in the third or fifth week after EBRT or after it is finished. Due to detrimental effect on the rate of cure, all radiation therapy should be finished in 8 weeks, and treatment breaks are discouraged [31].

D. Advanced/ Metastatic cervical cancer (stage IV B):

The cervix is no longer the site of cervical cancer that has spread to different tissues or organs. The illness is well advanced. Depending on aa variety of factors, possibility for treatment involve immunotherapy, radiation therapy, Chemotherapy and surgery [32].

a) Chemotherapy: 80% of cervical malignancies have squamous histology, whereas adenocarcinomas account for a lowest percentage. It's unclear how chemotherapy will affect the behaviour of adenocarcinomas and squamous cell differently or similarly [33].

Single agent:

- For metastatic cervical cancer, the authorized single agent standard treatment has been cisplatin at a dosage of 50 mg/m2 every 21 days with comparable PES and OS and less toxicity, this regimen has historically has been Cisplatin at 100 mg/m2 every 21 days or 20 mg/m2 for five straight days every 21 days. Both carboplatin and iproplatin appeared to be less effective than cisplatin un a randomized experiment, with iproplatin being noticeable more toxic.
- A number of medications, including platinum, have been investigated to be utilized as a single agent chemotherapy in cases of cervical squamous cell carcinoma that is progressed recurrent, or persistence. These include vinorelbine, ifosfamid, irinotecan, gemcitabine, topotecan, paclitaxel, and mitomycin C. Two topotecan dosage regimens were examined: a) A 21-day cycle of 1.5mg/m2 given for 5 days in a row; b) A28-day cycle of 3.0 mg/m2 given on days 1,8, and 15. The overall response rate is varied between 8.0% and 17.0%, with paclitaxel exhibiting a higher rate.
- In a non-squamous, paclitaxel and vinorelbine have all been used in non-squamous Cervical cancer; response rates have been 4.5%, 31.0%, and 7.1% respectively.

Platinum doublet:

- Phase III studies include a cisplatin containing doublet including pototecan and paclitaxel, with encouraging outcomes. Remarkably, no patient in the topotecan doublet has previously had chemotherapy. Gemcitabine was an exception, since it's efficacy in the cisplatin doublet was rather low in individuals with the cervix squamous cell carcinoma that had already had treatment.

Nonplatinum doublet:

- Using paclitaxel (175mg/m2 on day 1) and topotecan (1mg/m2 on day 1 through 21) were used in a 21 day experiment conducted by Tiersten et al. With assistance from granulocyte colony stimulating factor. Although patients frequently encountered grade ¾ toxicities, including as hemophilia, leukopenia, thrombocytopenia, neurological damege, and diarrhea, the total response rate was 54%.

b) Targeted therapies:

- A number of molecularly targeted treatment, such as tyrosine kinase inhibitors (TKI) , angiogenesis inhibitors, and anti- EGGR antibodies, are being developed for use in treatment of metastatic cervical cancer.
- The vascular endothelial growth factor (VEGF) inhibitor bevacizumab has only had one phase III trial with encouraging outcomes.

Angiogenesis inhibitor:

- A humanized antibody called bevacizumab (Avastin; Genentech) proved effective in recurrent cervical cancer in second and third lines of therapy.
- Pazopanib is a potent and highly specific multi targeted receptor TKI of platelet. Lapatinib, also known as Tykerb/Tgverb from GlaxoSmithKline, is a dual TKI that acts on the EGFR and HER2/neu pathway. Patient were randomized 1:1:1 to receive 800mg/d of pazopanib, 1500mg/d of lapatinib, or 1000 mg of lapatinib Plus 400mg of pazopanib or 1500mg of lapatinib Plus 800mg of pazopanib once daily. In the pazopanib and lapatinib group. In 12% and 9% of patients, accordingly grade 4 diarrhea was noted.

Anti EGFR antibodies:

- Experiment have been conducted on cetuximab alone, in conjunction with cisplatin, or in conjunction with topotecan. Following the 400mg/m2 first dosage, 250mg/m2 is administered weekly. When more drugs were added, cetuximab's toxicity rose and it's efficacy in combination treatment was only moderate.

Other agents:

- Celecoxib and other cyclooxygenase-2 inhibitors were tested in cases of advanced cervical cancer that was left untreated. Hematologic abnormalities were often observed whenever simultaneously chemoradiation and 400 mg/ day of celecoxib were administered.
- In the phase I research, magnesium valproate, also known as valproic acid, a histone deacetylase inhibitor, demonstrated tolerance at dosage ranging from 20mg/kg to 40mg/kg during chemoradiation.

c) Immunotherapy or immunomodulatory therapy:

- Targeting the viral proteins may result in strong antitumor immune response, given that nearly all cervical cancer and their genesis are associated with high-risk HPV infection. Additional biologic response modifiers have been observed to enhance the immune response of immunotherapy, such as Z-100, Ok-432, (1-3) β-D-glucan and heat killed lactobacillus case [34].

E. Recurrent cervical cancer:

Cancer that reappears after treatment is referred to as recurrent cancer. Cancer can recur locally, that is in the cervix, uterus, or in close proximity to the pelvic organs, or it has the potential to spread to other areas like the pulmonary system or skeleton. [35].

- Prevent recurrence: Optimizing the first course of treatment may generally yield more benefits than intensive salvage therapy or purpose post treatment observation. The management of cervical cancer has lately been subject of substantial investigation into multimodality techniques. In many randomized controlled studies for locally advanced cervical cancer, concurrent chemotherapy pluse radiation treatment significantly lower the proportional chance of failure or demise compared to radiation therapy alone. Adjuvant therapy has shown mixed outcomes for early stage patient who are at high risk of not responding to therapy and are undergoing radical surgery.
- Post therapy surveillance: Regardless of the kind of treatment used, the median time to recurrence is often short more than 75% do so within 3 years after the initial diagnosis. Post therapy monitoring is to monitor treatment problems, evaluate outcome and identify recurrence early on. We follow a 3 months routine for post

therapy surveillance, which is followed by r months visit, and yearly during the third year, 6 monthly visit between the third and fifth years, and yearly visits after that. Every visit includes a review of the patient's medical history, physical and pelvic exam, pap smear, and serum tumor markers (carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC- Ag) for squamous cell carcinoma, CA125 and CEA for adenocarcinoma, and SCC- Ag, CEA, and CA125 for adenosquamouse carcinoma). Annual chest X-ray examination is recommended for asymptomatic individuals, and CT-MRI scans are done annually for the first three years in high-risk group or as clinically necessary.

- Prognostic factors after failed primary treatment: salvage therapy (surgery, irradiation with or without Chemotherapy, or both) to reset able pelvic or limited extra pelvic metastases may result in a subsequent cure in certain patient who underwent radiation therapy or initial major surgery but still has cancer that is not going away. The known predictors of prognosis following recurrence includes primary therapy, relapse pattern and presenting features (initial stage, histological type, or lymph node metastases).
- Pelvic Exenteration: for patient with clean pelvic sidewalls and no metastatic tumors elsewhere who develop a central pelvic relapse, pelvic Exenteration is typically required after final radiation therapy or surgery combined with adjuvant radiation therapy has failed. Result varies depending on which patient are close. It is feasible to achieve continuous urine diversion with manageable short- and long-term complications. Exenteration is known to be contraindicated in cases with multiple vaginal and/or para-aortic regional tumors, peritoneal propagation, upper gastrointestinal tumor enlargement, and distant metastases. However, in a sizeable percent of individuals who have had intentional preoperative study evaluation, the research for exenteration is aborted. The surgery was cancelled for a variety of reasons, such as parametrial fixation, nodal metastases, and peritoneal illness. Reirradiation may be possible in certain cases for superficial late recurrence in the vagina or cervix. For minor uterine and/or vaginal recurrence with substantial operation morbidity, radical hysterectomy with or without pelvic nodes dissection is seen to be a viable treatment option. With a high failure rate in the pelvic who have an initial FIGO stage of IIB or below cannot be save by further exenteration.
- The function of chemotherapy for cervical cancer that reappears: In basic terms, Chemotherapy is palliative on its own. Cisplatin continues to be the most effective single agent. In addition to 5- Fluorouracil, other active medicines for cervical cancer include doxorubicin/epirubicin, ifosfamid, dibromodulcitol, CP-11, paclitaxel, gemcitabine, topotecan. Combination treatment often produced larger response rate and progression free period compared to only cisplatin, but did not significantly enhance overall survival (>5 years) in two patients: one with supraclavicular lymph node metastasis from treatment alone, and the other with multiple lung metastases [36].

F. Cervical cancer during pregnancy:

- Patients who may have an invasive cervical neoplasia lesion and are pregnant: pregnant individual with suspected cervical lesion should have incision biopsies performed to look into them. Given that the gadolinium is linked to pediatrics rheumatological illnesses and neonatal mortality, after a cancer is diagnosed, imaging staging should preferably be performed using a chest x-ray that protects the abdomen and magnetic resonance

imaging of the whole abdomen without contrast. An ultrasound of the whole abdomen can be done in the absence of magnetic resonance imaging, with special attention paid to the kidneys and urinary system.

- Pregnant individuals with stage IA1 or stage II cervical carcinoma who are pregnant are recommended to have conization or other conservative surgical treatment between weeks 14 and 22 of their pregnancy. Reduced bleeding and morbidity are associated with high frequency surgical conization. It is questionable if cerclage is necessary.
- Pregnant patients with advanced locally diagnosed cervical cancer: Neoadjuvant chemotherapeutic agents, beginning after 14 weeks of pregnancy, is recommended every 3 weeks using carboplatin and paclitaxel. Treatment should be continued until 34 or 35 weeks, and delivery should occur at term, if there is no progression. 2 weeks after birth, radiotherapy can begin.
- Pregnant patients with stage IVB cervical cancer: Immune- mediated therapies employing synthetic humanized monoclonal antibodies shouldn't endanger pregnancy, such as pembrolizumab and bevacizumab. Early referral to palliative care for the treatment of pain and other symptoms is crucial as it comes to advanced and metastatic disease since it not only increases the patient's probability of survival but also enhances their quality of life [37].

G. Complication and side effects of treatment:

- Radiation related complication: The normal tissue in the immediate vicinity of the radiation treatment site, including the bladder, intestine, and perineal skin, are frequently impacted. Diarrhea, abdominal cramps, soreness in the lower abdomen and bleeding are examples of acute unfavorable gastrointestinal consequences. Giving Atropine sulfate or loperamide will often manage diarrhea. Proctitis symptoms are treated with little enemas that includes steroids. Dysuria, frequency, and nocturia can also result from cystourethritis. Antispasmodic usually help to reduce symptoms. Urine should always be checked for infection. As soon as urinary tract infection is identified, treatment has to start. The perineum has to be kept in good skin hygiene. In the event of erythema or desquamation, topical lotion needs to be used. Radiation therapy late sequelae often show up 1-4 years after the first treatment. Rectal or vaginal stenosis, small intestinal blockage, malabsorption, radiation enteritis, and persistent cystitis are the main after effects.
- Premature Menopause: Menopause normally start around the ages of 45 and 55. If ovaries are removed during cancer treatment, chemotherapy, or a radiation therapy, period may cease or become irregular, and may experience early Menopause. The beginning of menopause is frequently treated with hormones replacement therapy (HRT), frequently in conjunction with contraception.
- Concentrating of vagina: Radiation therapy frequently causes vagina narrower. Sexual activity may become uncomfortable or challenging as a result. This may cause discomfort or difficulty sexual activity. There are two methods of treating a constricted vagina; a hormone cream that you apply to your vagina to make it drier; this will facilitate intercourse; a vaginal dilator.
- Lymphoedema: The lymphatic system includes lymph nodes. The lymphatic system removes extra fluid from the tissues in body. You may experience a build-up of fluid in the tissue if your lymphatic system is compromised. This results in the swelling of several bodily parts. Leg will often swell if you have cervical

cancer. We refer to this as lymphoedema. Your legs and pelvic may enlarge as a result of pelvic radiotherapy. Compression clothing and specialized bandage can also be helpful [38]

- Surgical complications: Due to partial detrusor muscle denervation, urinary impairment is the most common side effects after radical hysterectomy. Additional problem including intestinal blockage, bleeding, infection, ureterovaginal fistula, structure and rectovaginal fistulas, intestinal fibrosis and rectosigmoid colon fibrosis. These individuals occasionally undergo invasive surgeries (such as nephrostomies or diverting colostomies) in an effort to enhance their to enhance their quality of life [25].
- Urological complication: Although the precise frequency of lower urinary tract dysfunction following cervical cancer treatment is unknown, it has declined over the previous 20 years. Urological disorders that frequently arise following radical surgery include low bladder compliance, incontinence, hyperactivity of the detrusor, and hypocontractility of the bladder. Following a radical hysterectomy, lower urinary tract dysfunction can be minimized with the use of neuroanatomical knowledge and concurrent never sparing surgery. Urological problem caused by radiation include irradiation cystitis, bladder poor compliance, stenosis, and formation of fistula.[39].

H. Future direction of cervical cancer management:

- Immunotherapy for cervical cancer: Immunotherapy that targets HPV tumor suppressors has being investigated has a possible cutting-edge cervical cancer treatment, and the results look very promising. One benefits of this treatment it it's capacity to specifically target malignant precancerous and malignant cervical epithelial cells which generate HPV tumor suppressors. This strategy has incresed popularity and produced a number of laboratory and clinical advancement, such as the creation of vaccines, inhibitors or checkpoint blockers, and adoptive T-cell treatment for cervical cancer. Numerous of these immunotherapies are undergoing clinical trials, and their success rates vary. A clinical experiment including a therapeutic HPV-16 specific vaccination shown its ability to target pre-invasive dysplastic lesion, resulting in a 79% response rate in vulvar intraepithelial carcinoma patients with grade 3 HPV positive. Additional vaccination that targets therapy HPV-16 and HPV-18 oncoproteins E6 and E7 specifically can be depend on peptide and protein or live vectors, such as bacterial and viral vectors. These are summarized below

Table.5. immunotherapies for cervical cancer treatment

Immunotherapy	Precise objective	Medicinal substance	CIN/ cervical cancer stage	Result
vaccination	HPV-16 E7 combination protein	ADXS11-001(bacterial)	Sophisticated/ enduring/ frequent	Compared to the present chemotherapeutic drug, cisplatin, there has been significant

				clinical activity with documented longer life, tumor responses, and stability of recurrent illness.
	HPV- 16 E6 and E7 peptide concentration	TA-HPV	Advancing	Well, tolerated, with 13.8- 37.5% of patient developing HPV-specific cytotoxic T cells following vaccination, and 27.6- 37.5% of patient developing HPV-specific solution that were probably beneficial therapeutically.
		SGN- 00101	Superior CIN	The immune response connection with generated lesion regression point to enhanced immunogenicity.
	HPV-16 E7 HLA-A2 limited peptide	ZYC101a	Superior CIN	All patients found it to be well tolerated, and in women under 25, it helped to promote the clearance of CIN 2/3
	PD-1/PD-L1	Pembrolizumab	PD-L1 positive tumor's	Demonstrated a stronger anti-

Immune checkpoint inhibitor				cancer effect and an improved toxicity profile.
		Nivolumab	Advanced /recurrent	Warrant more research because none of the patients under study showed the presence of any new safety signs.
		Cemiplimab	Recurrent/ metastatic	Proven therapeutic efficacy and safety profile for platinum and taxan doublet resistance/ intolerant patients that is similar to that seen with the other PD-1 inhibitor
		Balstilimab	Recurrent /metastatic	Produced reasonable safety as well as significant and long-lasting clinical activity.
Adoptive T cell therapy (ACT)	Tumor-penetrate lymphocytes	LN-145 TIL	Recurring/ enduring /metastatic	An adequate safety and efficacy profile results in an objective response rate of 44% and an 89% disease control rate in patient

				who have previously undergone therapy for cervical cancer. [40]

IX. Conclusion:

The therapy of cervical cancer has come a long way, with a variety of choices available depend on the patient's age, general health, and desire to maintain fertility as well as disease's stage. Treatment available now include: surgery, radiation therapy, Chemotherapy, targeted therapy and immunotherapy, palliative care. Cervical cancer incidence is declining thanks to these treatments as well as rising HPV vaccination rates, which is a key contributing factor in the disease. However, socioeconomic status and location may have an impact on access to this cutting-edge treatment; this is especially true in India, where access to healthcare varies between urban and rural areas. Government initiative in India is aimed at increasing awareness and enhancing screening coverage since early diagnosis through routine Pap smear and HIV screening is vital. Early detection of cervical cancer significantly improves prognosis and treatment chance. Key detection includes pap smear test and HPV testing. Benefit includes increased survival rates, less aggressive treatment, reduced healthcare cost, and the role of vaccination. Compressive care addresses patients holistic need, including a multidisciplinary approach, tailored treatment plans, supportive care, psychological support, follow up, and survivorship care. Government and healthcare system play a vital role in promoting awareness and access to cervical cancer screening and vaccination programs, especially in low resource settings. Vaccination help prevent the infection leading to cervical cancer reducing its incidence over time. Advancement in immunotherapy, targeted therapies, and minimally invasive techniques are expected to significantly improve cervical cancer treatment, improving Survival rates, reducing side effects, and offering personalized options.

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