

REVIEW ARTICLE



A Review on Contemporary Paradigms and Mechanistic Advances in the Therapeutic Management of Cervical Cancer

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Publication history: Received on 12th June 2026; Revised on 20th July 2026; Accepted on 22nd July 2026

Article DOI: 10.69613/aw11zz66

Abstract: Cervical cancer is the primary cause of gynecologic oncologic mortality internationally, disproportionately affecting developing economies lacking systematic screening and vaccination infrastructures. Carcinogenesis is driven by persistent integration of high-risk human papillomaviruses, wherein oncoproteins E6 and E7 break cell-cycle checkpoints via ubiquitination of p53 and functional inactivation of the retinoblastoma protein. While historical interventions relied primarily on radical extirpative surgery for early-stage disease and cisplatin-based concurrent chemoradiotherapy for locally advanced stages, the therapeutic landscape has evolved substantially. The 2018 revision of the International Federation of Gynecology and Obstetrics staging system fundamentally altered clinical prognostication by codifying radiological and pathological lymph node status alongside three-dimensional metric stratifications. Image-guided adaptive brachytherapy has elevated local control rates while attenuating gastrointestinal and genitourinary toxicities. Systemic intervention for persistent, recurrent, or metastatic disease has transitioned from cytotoxic doublets to targeted regimens incorporating anti-angiogenic monoclonal antibodies, immune checkpoint blockades targeting programmed cell death protein 1, and antibody-drug conjugates directed against cell-surface antigens such as tissue factor. Recent biological treatments include cell cycle checkpoint inhibition via Wee1 kinase inhibition, synthetic lethality exploiting poly (ADP-ribose) polymerase inhibition in DNA repair pathways, and autologous tumor-infiltrating lymphocyte transfer platforms. The aim of this review is to discuss about the contemporary management standards, translating landmark Phase III clinical trials into oncologic practice including prevention, definitive local targeting, and systemic drug therapies.

Keywords: Cervical Carcinoma; Human Papillomavirus; Chemoradiotherapy; Immune Checkpoint Blockade; Antibody-Drug Conjugates.

1. Introduction

Persistent infection with oncogenic, high-risk human papillomaviruses (hrHPV) is established as the obligate etiological event in the pathogenesis of invasive cervical carcinoma [1]. Epidemiologically, cervical cancer remains the fourth most frequently diagnosed malignancy and the fourth leading contributor to female cancer mortality globally, accounting for over 660,000 incident cases and approximately 350,000 deaths annually [2]. The geographic distribution of this disease reflects profound socioeconomic gradients. Approximately 85% to 90% of the worldwide burden occurs in low- and middle-income countries, where organized, population-based primary and secondary preventive programs are severely constrained or absent [2, 3]. In high-resource nations with institutionalized cytologic and molecular screening frameworks, cervical cancer incidence and mortality have dropped considerably over recent decades, shifting the primary presentation toward younger, premenopausal demographics diagnosed with early-stage, surgically treatable disease [3, 4].

The fundamental causal link between mucosal viral infection and cervical malignant transformation was established following the isolation and genomic sequencing of HPV types 16 and 18 by Harald zur Hausen [5]. Subsequent molecular and epidemiological evaluations have indicated that upwards of 99% of all cervical carcinomas harbor detectable hrHPV genomes [6]. Sexual intercourse represents the primary vehicle of horizontal viral transmission, with cumulative lifetime exposure rates exceeding 80% among sexually active individuals [7].

Cofactors modulating the likelihood of genomic persistence and subsequent neoplastic transformation include concurrent human immunodeficiency virus (HIV) co-infection, therapeutic or acquired immunosuppression, high parity, early age at sexual debut, and tobacco exposure [8]. Systematic prospective cohorts, including the European Prospective Investigation into Cancer and Nutrition (EPIC), have shown that tobacco smoking functions as an independent, dose-dependent chemical cofactor, approximately doubling

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the risk of high-grade intraepithelial lesions and invasive disease through the mutagenic actions of locally concentrated tobacco metabolites such as nicotine and cotinine within the cervical mucus [9].

For nearly two decades, the therapeutic benchmark for cervical cancer was bifurcated strictly according to anatomic staging: radical surgical intervention for early-stage disease and cisplatin-based concurrent chemoradiotherapy (CCRT) for locally advanced disease [10]. However, long-term survival for advanced, recurrent, and metastatic cohorts remained plateaued under standard cytotoxic regimens. Understanding the viral-host genomic interactions, immune escape microenvironments, and aberrant signaling cascades in cervical carcinoma has catalyzed modern targeted biologicals, antibody-drug conjugates, image-guided volumetric radiation modalities, and immune checkpoint blockades [11, 12].

2. Pathogenesis and Carcinogenesis

2.1. Histopathological Subtypes

Malignant cervical neoplasms arise predominantly within the squamocolumnar junction (SCJ), an anatomically dynamic transition zone where the stratified non-keratinizing squamous epithelium of the ectocervix interfaces with the simple mucin-secreting columnar epithelium of the endocervical canal [13]. Continual squamous metaplasia renders this region uniquely susceptible to micro-abrasions that expose underlying basal epithelial cells to viral entry [14]. Squamous cell carcinoma (SCC) comprises roughly 75% to 80% of all primary cervical malignancies, whereas invasive adenocarcinoma, originating within endocervical glandular crypts, accounts for 20% to 25% of cases [15]. Other rare subtypes, including adenosquamous carcinoma, neuroendocrine cervical carcinoma, and clear cell carcinoma, comprise the remainder [15]. Over recent decades, the absolute and relative incidence of endocervical adenocarcinoma has risen, particularly among younger cohorts, partly due to the limitations of standard exfoliative cervical cytology in sampling high endocervical glandular crypts [16].

2.2. Viral Oncogenesis

The human papillomavirus possesses a circular double-stranded DNA genome of approximately 8,000 base pairs encoding early regulatory proteins (E1, E2, E4, E5, E6, E7) and late structural capsid proteins (L1, L2) [17]. In transient, self-limiting productive infections, the viral genome is maintained episomally, replicating autonomously without significant disruption to the host cellular genome [17, 18]. Malignant progression is initiated when persistent viral infection culminates in the integration of the viral DNA into the host genome, often causing the deletion or functional silencing of the viral transcriptional repressor gene *E2* [18]. Loss of *E2* expression leads to the continuous, uninhibited transcription of the primary viral oncoproteins, E6 and E7 [19].

The E6 oncoprotein complexes with an endogenous cellular E3 ubiquitin-protein ligase known as E6-associated protein (E6AP). This active E6-E6AP heterodimer directly binds the core domain of the p53 tumor suppressor protein, orchestrating its rapid polyubiquitination and targeted degradation via the 26S proteasome [20]. The depletion of functional p53 abrogates transcription of the cyclin-dependent kinase inhibitor p21 (CIP1/WAF1), preventing G1/S and G2/M arrest in response to DNA damage and disarming pro-apoptotic signaling pathways [20, 21]. Concurrently, E6 activates human telomerase reverse transcriptase (hTERT), preventing critical telomere erosion and conferring cellular immortality [21].

The E7 oncoprotein accelerates cell-cycle progression by binding to and inactivating the hypophosphorylated retinoblastoma tumor suppressor protein (pRb), as well as related pocket proteins p107 and p130 [22]. In normal quiescent cells, hypophosphorylated pRb sequestered E2F transcription factors to halt progression from G1 into S phase. The binding of E7 induces the dissociation of the pRb-E2F complex and targets pRb for proteasomal destruction [22, 23]. Liberated E2F family proteins drive the constitutive transcription of genes essential for DNA synthesis and mitotic entry, including cyclin E, cyclin A, and the cyclin-dependent kinase inhibitor p16INK4a [23]. Because downstream negative-feedback mechanisms are abolished by pRb degradation, p16INK4a accumulates at markedly high levels in the cytoplasm and nucleus, establishing p16INK4a as an established surrogate immunohistochemical biomarker for hrHPV E7-mediated transformation [24].

2.3. Precancerous Lesions and the Dynamics of Progression

Squamous cervical neoplasia progresses along a continuum of morphological alterations classified histopathologically as Cervical Intraepithelial Neoplasia (CIN) or by cytologic terminology under the Bethesda System as Low-Grade and High-Grade Squamous Intraepithelial Lesions (LSIL and HSIL) [25].

2.3.1. CIN1 (Low-grade dysplasia / LSIL)

Characterized by mild nuclear atypia and hyperchromasia localized strictly to the lower third of the squamous epithelium. This lesion reflects a cytopathic, productive HPV infection with high rates of spontaneous clearance (approximately 60% to 70% resolve within two years via host cellular immunity) [25, 26].

2.3.2. CIN2 (Moderate dysplasia / HSIL)

Exhibits atypical, pleomorphic basal-like cells expanding through the lower two-thirds of the epithelial thickness, with variable clonal aneuploidy and higher rates of HPV genomic integration [26].

2.3.3. CIN3 (Severe dysplasia and Carcinoma in Situ / HSIL)

Features full-thickness cytologic atypia, loss of cellular maturation, high nuclear-to-cytoplasmic ratios, and aberrant mitotic figures extending to the epithelial surface [26]. Progression from CIN3 to invasive microcarcinoma involves degradation of the epithelial basement membrane mediated by matrix metalloproteinases (MMP-2, MMP-9), providing the neoplastic cells entry into vascular and lymphatic channels within the underlying cervical stroma [27].

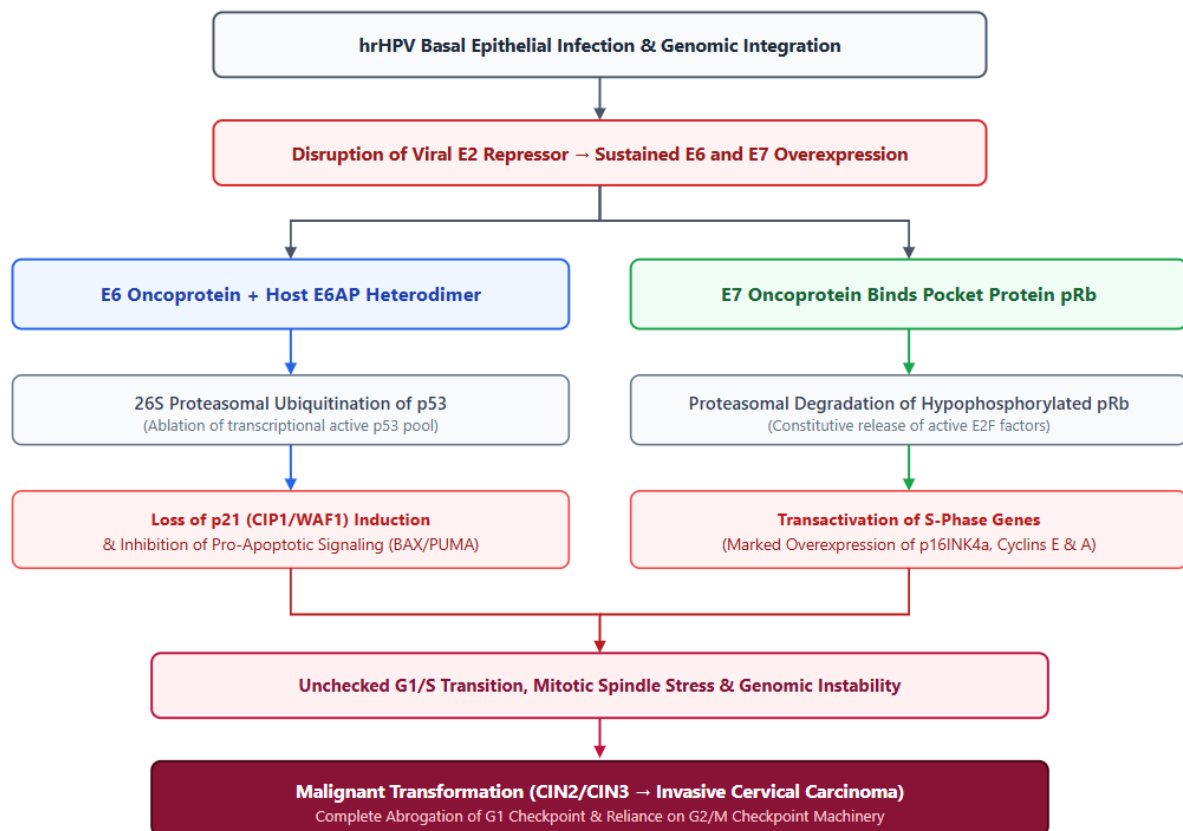


Figure 1. Pathophysiology of HPV progression involving hrHPV E6- and E7-Mediated Cell Cycle Dysregulation

3. Screening and Primary Prevention

3.1. Prophylaxis through Recombinant Human Papillomavirus Vaccines

Primary prevention of cervical carcinoma rests on the widespread distribution of prophylactic recombinant virus-like particle (VLP) vaccines assembled from the major capsid protein L1 [28]. Recombinantly expressed L1 spontaneously self-assembles into non-infectious, non-oncogenic, highly immunogenic empty viral capsids that elicit neutralizing IgG antibody titers several orders of magnitude higher than those produced following natural mucosal infection [28, 29].

Three major prophylactic vaccines have gained worldwide regulatory licensure:

3.1.1. Bivalent Vaccine (*Cervarix*)

Targets high-risk oncogenic types HPV-16 and HPV-18, formulated with the AS04 adjuvant system (aluminum hydroxide with 3-O-desacyl-4'-monophosphoryl lipid A) to elicit sustained antibody titers [30].

3.1.2. Quadrivalent Vaccine (*Gardasil*)

Targets HPV-16 and HPV-18, as well as low-risk types HPV-6 and HPV-11 (the primary causative agents of benign anogenital condylomata acuminata), using an amorphous aluminum hydroxyphosphate sulfate adjuvant [31].

3.1.3. Nonavalent Vaccine (*Gardasil 9*)

Broadens protective coverage by incorporating VLPs against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58. By covering seven distinct hrHPV genotypes, this formulation extends theoretical prophylactic coverage from 70% to approximately 90% of all invasive cervical malignancies globally [32]. The target demographic established by the World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP) prioritizes girls and boys aged 9 to 14 prior to sexual debut and potential viral exposure [33]. Clinical trials and real-world population data indicate that two-dose regimens administered at 0 and 6–12 months produce non-inferior immunogenicity in children aged 9–14 compared to historical three-dose schedules in older adolescents [34]. For immunocompromised individuals, including people living with HIV, standard three-dose regimens (0, 1–2, and 6 months) remain recommended [33, 34]. Catch-up vaccination strategies are typically extended through age 26, with shared clinical decision-making applied for adults aged 27 through 45 based on prospective exposure risks [34].

3.2. Secondary Prevention through Cytologic and Molecular Screening

Secondary prevention focuses on detecting and managing high-grade precancerous intraepithelial lesions before invasion occurs. The conventional Papanicolaou (Pap) smear and liquid-based cytology (LBC) detect cytomorphologic manifestations of dysplasia [35]. While cytology programs have reduced cervical cancer mortality where broad laboratory quality controls are sustained, the sensitivity of single-application exfoliative cytology for CIN2+ is modest (50% to 65%), requiring frequent, multi-year screening cycles [35, 36]. To address these limitations, molecular testing utilizing nucleic acid amplification (e.g., real-time PCR or target amplification assays) to detect high-risk HPV DNA or RNA has been validated as an alternative primary screening modality [36, 37]. Molecular hrHPV assays show greater analytical sensitivity (exceeding 90% to 95%) for identifying CIN3 and invasive disease compared to primary cytology [37].

The primary strategies applied in contemporary clinical practice include:

3.2.1. Primary hrHPV DNA Screening

Recommended by international clinical guidelines (including the WHO, American Cancer Society, and ASCCP) every 5 years, starting at age 25 or 30. A negative hrHPV test provides a longer reassuring negative predictive value than negative cytology alone [37, 38].

3.2.2. Cytology-Based Screening

Standard Pap or LBC performed every 3 years from age 21 to 29, or continued through age 65 where molecular assays are unavailable [38].

3.2.3. Co-Testing (*Simultaneous Cytology and hrHPV Testing*)

Recommended every 5 years for individuals aged 30 through 65 in several regional guidelines, balancing sensitivity with specific reflexive algorithms for discordant results (e.g., hrHPV-positive, cytology-negative) [38, 39].

3.3. Colposcopy, Biomarkers, and Triage of Abnormal Findings

Patients screening positive for high-risk HPV-16 or HPV-18, or displaying persistent non-16/18 hrHPV infection with cytologic abnormalities (Atypical Squamous Cells of Undetermined Significance [ASC-US] or higher), are directed to diagnostic colposcopy

[39]. Colposcopic evaluation uses acetic acid application and Lugol's iodine staining to highlight areas of abnormal vascularity (punctuation, mosaicism, atypical branching vessels) and aceto-white changes that guide directed biopsies [39, 40]. Dual-staining for p16INK4a and the cellular proliferation marker Ki-67 has emerged as a reliable ancillary triage tool [40]. Simultaneous overexpression of both biomarkers indicates cell-cycle checkpoint disruption (E7-mediated pRb loss leading to p16INK4a overproduction) occurring concurrently with active mitotic division (Ki-67 expression). This helps differentiate true transforming dysplasias (CIN2+) from benign metaplastic or reactive changes, reducing diagnostic ambiguity and unnecessary excisional interventions [40, 41].

4. Diagnosis, Clinical Staging, and the FIGO 2018 System

4.1. Diagnostic Evaluation and Pre-Therapeutic Imaging

Definitive diagnosis requires histological verification via colposcopically directed punch biopsy, endocervical curettage, or diagnostic excisional procedures, including Loop Electrosurgical Excision Procedure (LEEP) or Cold-Knife Conization (CKC) [42]. Once invasive carcinoma is verified, accurate pre-therapeutic staging is essential for stratifying patients between primary radical extirpative surgery and definitive organ-preserving chemoradiation [43].

Unlike historical approaches, modern management relies on cross-sectional diagnostic imaging:

4.1.1. Pelvic Magnetic Resonance Imaging (MRI)

The gold standard modality for delineating primary tumor dimensions, depth of cervical stromal invasion, distance to the internal os, involvement of the vaginal fornices, and lateral extension into the parametrial tissues [44].

4.1.2. Positron Emission Tomography–Computed Tomography (^{18}F -FDG PET/CT)

The preferred systemic modality for detecting occult pelvic and para-aortic lymph node metastases, as well as unexpected distant peritoneal, pulmonary, or skeletal dissemination [45].

4.1.3. Contrast-Enhanced Computed Tomography (CECT) of Abdomen and Pelvis

Utilized when PET/CT is inaccessible to evaluate hydronephrosis, ureteral obstruction, and macroscopic retroperitoneal lymphadenopathy [44, 45].

4.2. FIGO 2018 Staging System

Historically, the FIGO staging system was purely clinical, relying on physical examination, cystoscopy, proctosigmoidoscopy, and plain radiography to maintain global applicability in resource-constrained environments [46]. However, this clinical framework frequently understaged nodal disease and failed to reflect true anatomic disease burden. The modern FIGO 2018 staging system formalized a major paradigm shift by explicitly permitting the integration of advanced imaging modalities (ultrasonography, MRI, CT, PET/CT) and pathological assessments to assign stage, while formally introducing nodal status directly into Stage III [47]

Table 1. The 2018 FIGO Staging System for Cervical Carcinoma

FIGO 2018 Stage	Anatomical and Pathological Classification
Stage I	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded).
Stage IA	Invasive carcinoma that can be diagnosed only by microscopy, with a maximum depth of stromal invasion <5.0 mm.
Stage IA1	Measured stromal invasion <3.0 mm in depth.
Stage IA2	Measured stromal invasion ≥ 3.0 mm and <5.0 mm in depth.
Stage IB	Invasive carcinoma with measured stromal invasion ≥ 5.0 mm (greater than Stage IA), limited to the cervix uteri.
Stage IB1	Invasive carcinoma ≥ 5.0 mm depth of stromal invasion and <2.0 cm in greatest dimension.
Stage IB2	Invasive carcinoma ≥ 2.0 cm and <4.0 cm in greatest dimension.
Stage IB3	Invasive carcinoma ≥ 4.0 cm in greatest dimension.

FIGO 2018 Stage	Anatomical and Pathological Classification
Stage II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall.
Stage IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement.
Stage IIA1	Invasive carcinoma <4.0 cm in greatest dimension.
Stage IIA2	Invasive carcinoma ≥4.0 cm in greatest dimension.
Stage IIB	Carcinoma with clear parametrial invasion, but not extending onto the pelvic sidewall.
Stage III	The carcinoma involves the lower third of the vagina, extends to the pelvic wall, causes hydronephrosis/non-functioning kidney, and/or involves regional lymph nodes.
Stage IIIA	Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall.
Stage IIIB	Extension to the pelvic wall and/or causes hydronephrosis or non-functioning kidney.
Stage IIIC	Regional lymph node metastasis, irrespective of primary tumor size or local extent (designated by imaging [r] or pathology [p]).
Stage IIIC1	Metastasis to pelvic lymph nodes only.
Stage IIIC2	Metastasis to para-aortic lymph nodes.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IVA	Spread of the growth to adjacent pelvic organs (biopsy-proven mucosal invasion of bladder or rectum).
Stage IVB	Spread to distant organs (e.g., extrapelvic peritoneal spread, lung, liver, or bone metastases).

5. Surgical Management of Early-Stage Disease

5.1. Conservative, Fertility-Sparing Interventions

For reproductive-aged women with early-stage disease desiring preservation of childbearing capacity, fertility-sparing surgery offers oncologic safety without compromising clinical outcomes [48]:

5.1.1. Cervical Conization (Loop Electrosurgical Excision Procedure (LEEP) or Cold-Knife Conization)

Indicated for Stage IA1 disease in the absence of lymphovascular space invasion (LVSI). If margins are histopathologically negative for residual neoplasia or dysplasia, conization alone is definitive [48, 49]. If LVSI is present in Stage IA1, pelvic lymph node assessment via sentinel lymph node biopsy is mandatory [49].

5.1.2. Radical Trachelectomy (Abdominal, Vaginal, or Minimally Invasive)

The standard fertility-sparing procedure for Stage IA2 to IB1 lesions measuring <2 cm without involvement of the upper endocervical canal or pelvic lymphatics [50]. The operation resects the uterine cervix, upper 1 to 2 cm of the vagina, and medial parametrial tissue while preserving the uterine corpus, ascending uterine arteries, and adnexa. A cerclage suture is placed at the level of the internal os to provide mechanical competence for future pregnancies [50, 51].

5.2. Radical Hysterectomy and Surgical Management

For patients with early-stage disease (Stage IA1 with LVSI, IA2, IB1, IB2, and select IIA1) who do not desire fertility preservation, radical hysterectomy with bilateral pelvic lymphadenectomy represents standard local management [51, 52]. The Querleu-Morrow classification categorizes radical hysterectomy based on lateral parametrial, paracervical, and vaginal margin clearance:

Type A: Minimal resection of paracervix; typical for Stage IA1 disease.

Type B: Partial resection of the paracervical and vesicouterine ligaments down to the ureter; provides negative surgical margins for microinvasive Stage IA2/IB1 disease while protecting autonomic innervation [52].

Type C: Complete transection of the uterosacral and vesicouterine ligaments at the pelvic sidewall and resection of the upper vaginal cuff; indicated for higher-risk primary tumors (IB1–IB2) [52, 53]. Nerve-sparing modifications (Type C1) dissect autonomic nerve pathways (hypogastric plexus, pelvic splanchnic nerves) to minimize long-term neurogenic bladder and rectal dysmotility [53].

5.3. Laparoscopic and Robotic Surgery Following the LACC Trial

Historically, minimally invasive surgery (MIS)—including conventional laparoscopy and robotic-assisted techniques—was widely embraced for radical hysterectomy based on retrospective evidence indicating shorter hospitalization, reduced blood loss, and lower perioperative complication rates [54].

However, the international, prospective, phase III LACC Trial (Laparoscopic Approach to Cervical Cancer) fundamentally altered surgical practice [55]. The trial showed that minimally invasive radical hysterectomy was associated with inferior rates of disease-free survival (DFS at 4.5 years: 86.0% vs. 96.5%; Hazard Ratio [HR] for recurrence = 3.74; 95% CI, 1.63–8.58) and overall survival (OS at 3 years: 93.8% vs. 99.0%; HR for death = 6.00; 95% CI, 1.77–20.30) compared with open abdominal radical hysterectomy [55, 56].

Multiple subsequent international registry studies corroborated these results. Proposed oncologic mechanisms responsible for the inferiority of MIS include:

1. The use of intrauterine manipulators, which can breach tumor integrity, leading to mechanical disruption and microscopic seedling into the peritoneal cavity [56].
2. The mechanical effects of CO₂ pneumoperitoneum, where positive intracavitary pressure may aerosolize tumor cells across the peritoneal surface [56, 57].
3. Intracorporeal colpotomy performed in an open gas environment, allowing loose malignant cells to shed directly into the pelvic cavity [57].

Following these findings, open abdominal radical hysterectomy remains the established clinical standard for early-stage cervical carcinoma across international guidelines (NCCN, ESGO). Minimally invasive procedures are generally restricted to institutional investigational protocols evaluating protective maneuvers (e.g., vaginal cuff closure prior to colpotomy, avoidance of intrauterine manipulators) [57, 58].

5.4. Sentinel Lymph Node Mapping and Ovarian Transposition

Sentinel lymph node (SLN) mapping using dual-tracer strategies (technetium-99m labeled nanocolloid combined with indocyanine green [ICG] under near-infrared fluorescence) has gained substantial validation [58]. Pathologic ultrastaging using serial sectioning and cytokeratin immunohistochemistry identifies low-volume micrometastases (0.2 mm to 2.0 mm) and isolated tumor cells (< 0.2 mm) that standard hematoxylin and eosin staining frequently overlooks [58, 59]. In patients with tumors < 2 cm, SLN mapping with complete pelvic lymphadenectomy performed upon mapping failure shows high diagnostic accuracy, helping spare node-negative women the morbidity of full retroperitoneal dissection (such as lower extremity lymphedema, lymphoceles, and neurovascular injury) [59].

Ovarian transposition (oophoropexy) involves mobilizing the ovaries and fallopian tubes on their infundibulopelvic vascular pedicles and securing them outside the anticipated pelvic radiation field (typically anterolaterally into the paracolic gutters above the iliac crests) [60]. This procedure is suitable for young, premenopausal patients with squamous cell histology undergoing radical surgery who face an intermediate-to-high risk of requiring adjuvant pelvic radiotherapy [60, 61]. Ovarian transposition preserves endogenous endocrine production and prevents premature iatrogenic menopause, although ovarian metastasis risks must be carefully weighed; this procedure is generally avoided in patients with primary endocervical adenocarcinoma due to higher rates of occult ovarian tropism [61].

6. Definitive and Adjuvant Radiotherapy Modalities

6.1. Concurrent Chemoradiotherapy (CCRT) for Locally Advanced Disease

For patients presenting with locally advanced cervical cancer (LACC; Stage IB3, IIA2, IIB, III, and IVA), definitive concurrent chemoradiotherapy (CCRT) represents the standard of care [62]. Radical extirpative surgery is contraindicated in these stages, as dual-modality interventions (radical surgery followed by postoperative adjuvant radiation) markedly increase severe gastrointestinal and genitourinary toxicities without conferring an overall survival advantage [62, 63].

The standard CCRT regimen combines external beam radiation therapy (EBRT) to the pelvis (and para-aortic nodes if involved) delivered concurrently with weekly radiosensitizing cisplatin administered intravenously at a dose of 40 mg/m² for 5 to 6 cycles [63]. The survival benefit of concurrent cisplatin was validated across multiple landmark Gynecologic Oncology Group (GOG) and Radiation Therapy Oncology Group (RTOG) randomized trials, showing absolute improvements in local control and overall

survival of 10% to 12% compared with radiation alone [64]. Cisplatin functions as a chemical radiosensitizer by inhibiting the repair of potentially lethal radiation-induced DNA double-strand breaks, synchronizing tumor cells into the radiosensitive G2/M phase of the cell cycle, and depleting endogenous free radical scavengers [64, 65].

6.2. External Beam Radiation: 3D-CRT, IMRT, and VMAT

External beam radiation therapy is delivered to a total pelvic dose of 45 to 50.4 Gy administered in daily fractions of 1.8 Gy, five days per week over roughly five weeks [66]. The transition from historical four-field box conventional three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) has improved dose distributions [66, 67].

IMRT and VMAT utilize computer-controlled multileaf collimators that dynamically modulate beam intensity, generating steep dose gradients around the clinical target volume (CTV)—which encompasses the primary gross cervical tumor, corpus uteri, parametria, upper third of the vagina, and regional draining nodal basins (obturator, internal iliac, external iliac, common iliac, and presacral nodes) [67]. By conforming the prescription isodose shell to complex targets, these modern modalities significantly reduce ionizing doses to adjacent organs-at-risk (OARs), particularly the small bowel, sigmoid colon, rectum, and urinary bladder [67, 68]. This preserves gastrointestinal and genitourinary function, lowering rates of acute radiation-induced enteritis, chronic bowel strictures, rectal bleeding, and radiation cystitis [68].

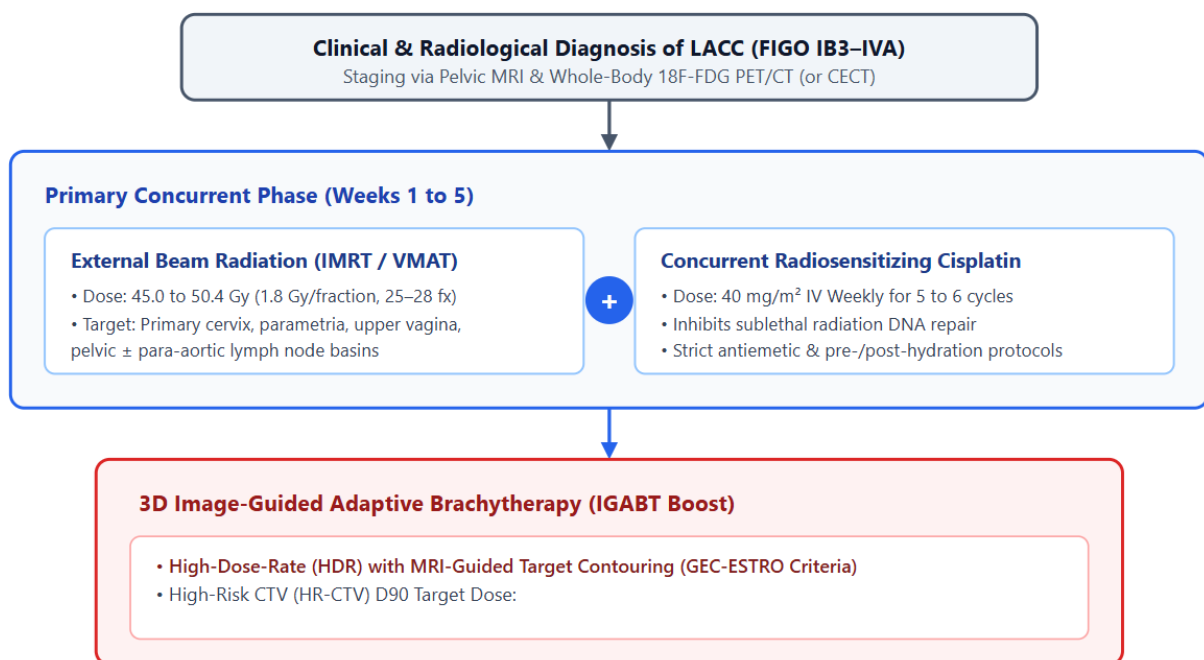


Figure 2. Definitive Chemoradiotherapeutic Management Framework for LACC (FIGO IB3-IVA)

6.3. Modern Image-Guided Adaptive Brachytherapy (IGABT)

Brachytherapy delivers high local doses directly to the residual cervical tumor volume while exploiting rapid inverse-square dose fall-off to spare surrounding normal tissues [69]. Intracavitary applicators (e.g., tandem and ring or tandem and ovoids), combined with interstitial needles where extensive lateral parametrial disease remains, allow precise target volume coverage [69, 70].

Over the past decade, historical two-dimensional point-A-based brachytherapy planning has been superseded by three-dimensional volumetric Image-Guided Adaptive Brachytherapy (IGABT), primarily guided by pelvic MRI [70]. The GEC-ESTRO (Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology) working group standardized target definitions for this approach:

6.3.1. High-Risk Clinical Target Volume (HR-CTV)

Involves the entire cervix along with any macroscopic residual disease visible at the time of brachytherapy; it carries a high risk of local recurrence and requires a dose of EQD2 ≥ 85 to 90 Gy[71].

6.3.2. Intermediate-Risk Clinical Target Volume (IR-CTV):

Includes the HR-CTV plus an anatomical safety margin accounting for the original tumor extent prior to CCRT; typically prescribed an EQD2 ≥ 60 Gy[71, 72]. The international multicenter observational RetroEMBRACE and prospective EMBRACE-I studies validated the clinical efficacy of MRI-guided IGABT in more than 1,400 patients [72, 73]. The results show an overall 5-year local control rate of 92%, with local control reaching 98% in Stage IB1/IB2, 93% in Stage IIB, and 84% in advanced Stage III/IVA disease [73]. These high local control rates correlated with an overall survival improvement of roughly 10% compared to historical controls treated with 2D plans, while simultaneously lowering severe Grade 3–4 rectal and urinary toxicities to under 5% [73, 74]. To avoid accelerated repopulation of radioresistant tumor clonogens, the entire duration of definitive CCRT—including both external beam radiation and the subsequent high-dose-rate (HDR) brachytherapy boost—must be completed within an overall treatment time of 56 days (8 weeks) [74, 75].

7. Systemic Chemotherapy and Sequencing

7.1. Cisplatin-Based Cytotoxic Doublets

For persistent, recurrent, or metastatic cervical carcinoma ineligible for curative local irradiation or surgical exenteration, systemic chemotherapy provides palliative disease control [76]. The randomized GOG-204 Phase III trial evaluated various cisplatin doublets, including combinations with paclitaxel, topotecan, gemcitabine, and vinorelbine [77]. The paclitaxel plus cisplatin doublet (135 mg/m² paclitaxel over 24 hours with 50 mg/m² cisplatin, or 175 mg/m² paclitaxel over 3 hours with 50 mg/m² cisplatin) indicated an objective response rate of roughly 29% and a median overall survival of 12.9 months [77, 78]. Carboplatin plus paclitaxel has shown comparable therapeutic efficacy with a favorable toxicity profile—notably producing less nephrotoxicity, neurotoxicity, and emetogenic morbidity—establishing it as a practical clinical doublet [78].

7.2. Sequencing Chemotherapy with Definitive CCRT

Historically, applying adjuvant systemic chemotherapy following the completion of primary CCRT failed to yield consistent survival benefits while causing substantial cumulative hematologic and gastrointestinal toxicities [79]. Conversely, the recent multicenter Phase III randomized INTERLACE trial evaluated whether dose-dense *induction* chemotherapy given immediately prior to CCRT improves survival outcomes in locally advanced cervical cancer [80].

In the INTERLACE trial, patients with Stage IB1 (node-positive) through IVA disease were randomized to receive standard definitive CCRT alone versus six cycles of weekly induction chemotherapy with carboplatin (AUC 2) plus paclitaxel (80 mg/m²) followed directly by CCRT starting at week 7 [80]. The findings show a statistically significant improvement:

Progression-Free Survival (PFS): 5-year PFS reached 73% in the induction arm compared with 64% in the CCRT-alone arm (HR = 0.65; 95% CI, 0.46–0.91; $p = 0.013$) [80].

Overall Survival (OS): 5-year OS was 80% with induction chemotherapy versus 72% with standard CCRT (HR = 0.67; 95% CI, 0.48–0.95; $p = 0.022$) [80].

These results indicate that induction chemotherapy administered in a dose-dense weekly fashion tackles micrometastatic dissemination early without significantly delaying or compromising definitive local radiation delivery.

8. Targeted Therapy and Inhibition of Angiogenesis

8.1. Vascular Endothelial Growth Factor (VEGF) and the GOG-240 Trial

Tumor-directed angiogenesis, driven by the sustained overexpression of Vascular Endothelial Growth Factor A (VEGF-A) via hypoxia-inducible factor 1-alpha (HIF-1 α) pathways and HPV oncoprotein signaling, supports disease progression and hematogenous dissemination in cervical carcinoma [81].

The landmark randomized Phase III GOG-240 trial evaluated the incorporation of the recombinant humanized anti-VEGF monoclonal antibody bevacizumab (15 mg/kg) combined with standard chemotherapy doublets (cisplatin plus paclitaxel, or topotecan plus paclitaxel) in recurrent, persistent, or metastatic cervical cancer [82]. The addition of bevacizumab to chemotherapy yielded:

Overall Survival: Median OS increased from 13.3 months to 16.8 months (HR = 0.77; 95% CI, 0.62–0.95; $p = 0.007$) [82].

Objective Response Rate (ORR): Increased from 36% with chemotherapy alone to 48% with the bevacizumab-containing regimen [82, 83].

While bevacizumab improved overall survival without diminishing patient-reported quality of life, its anti-angiogenic mechanism correlates with an increased incidence of hypertension (Grade ≥ 3 : 25% vs. 2%), venous thromboembolic events, and gastrointestinal/rectovaginal fistula formation (8.2% vs. 0.9%) [83]. Patients with prior full-dose pelvic radiation presenting with anterior or posterior vaginal wall tumor recurrence require careful clinical evaluation prior to initiating anti-VEGF therapy [83, 84].

9. Modern Immunotherapeutic Options

9.1. Immune Checkpoint Inhibition in First-Line Metastatic Disease

The immunogenic microenvironment of HPV-associated cervical carcinoma—characterized by foreign viral antigens alongside persistent tumor-mediated immunosuppression through the upregulation of Programmed Cell Death-1 (PD-1) and its ligand Programmed Cell Death-Ligand 1 (PD-L1)—provides a clear rationale for immune checkpoint blockade [85, 86].

The pivotal double-blind Phase III KEYNOTE-826 trial evaluated the addition of the anti-PD-1 monoclonal antibody pembrolizumab (200 mg every 3 weeks) to platinum-based chemotherapy (paclitaxel with cisplatin or carboplatin) with or without bevacizumab as first-line therapy for persistent, recurrent, or metastatic cervical cancer [87].

Among patients whose tumors expressed PD-L1 with a Combined Positive Score (CPS) ≥ 1 (which represented roughly 89% of the study cohort), the addition of pembrolizumab produced significant survival gains:

- PFS at 24 Months: 45.5% in the pembrolizumab group compared with 34.1% in the placebo group (HR = 0.62; 95% CI, 0.50–0.77; $p < 0.001$) [87].
- Overall Survival at 24 Months: 53.0% with pembrolizumab versus 41.7% with placebo (HR = 0.64; 95% CI, 0.50–0.81; $p < 0.001$) [87].
- Overall Survival in CPS ≥ 10 Population: HR for death was reduced further to 0.58 (95% CI, 0.44–0.78) [87, 88].

Based on these results, platinum plus paclitaxel combined with pembrolizumab, with or without bevacizumab, is established as the global preferred first-line standard of care for patients with PD-L1-positive (CPS ≥ 1) advanced, persistent, or metastatic cervical carcinoma.

9.2. Second-Line Monotherapy and Beyond: EMPOWER-Cervical 1

For patients with metastatic or recurrent cervical cancer whose disease progresses during or following initial platinum-based systemic therapy, subsequent options historically yielded low response rates ($< 15\%$) and median overall survival under 8 months [89].

The Phase III EMPOWER-Cervical 1 / GOG-3016 / ENGOT-cx9 trial evaluated cemiplimab, a high-affinity recombinant human IgG4 anti-PD-1 monoclonal antibody, versus investigator's choice single-agent chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in pretreated patients, irrespective of tumor PD-L1 expression [90].

The trial showed a clear survival benefit across histological cohorts:

Overall Survival (Full Cohort): Median OS was 12.0 months for cemiplimab compared with 8.5 months for cytotoxic chemotherapy (HR = 0.69; 95% CI, 0.56–0.84; $p < 0.001$) [90].

Overall Survival (Squamous Cell Carcinoma): Median OS was 11.1 months versus 8.8 months (HR = 0.73; 95% CI, 0.58–0.91; $p = 0.006$) [90].

Overall Survival (Adenocarcinoma/Adenosquamous): Median OS was 13.3 months versus 7.0 months (HR = 0.56; 95% CI, 0.36–0.85; $p < 0.005$) [90, 91].

Cemiplimab monotherapy established a new standard-of-care benchmark for second-line systemic treatment following first-line platinum failure, achieving regulatory approvals globally as an active single agent [91].

9.3. Checkpoint Blockade Integrated into Primary Chemoradiotherapy: KEYNOTE-A18 and CALLA

Given the immunomodulatory effects of high-dose ionizing radiation—including the release of tumor-associated neoantigens, up-regulation of MHC class I molecules, and stimulation of the STING-interferon pathway—integrating immune checkpoint blockade directly into primary definitive CCRT has been explored to reduce distant recurrences [92].

9.3.1. KEYNOTE-A18 (ENGOT-*cx11* / GOG-3047)

A randomized, double-blind Phase III trial evaluating concurrent and maintenance pembrolizumab alongside definitive cisplatin-based CCRT in high-risk locally advanced cervical cancer (FIGO 2018 Stage IB2–IIB node-positive, and Stage III–IVA regardless of nodal status) [93]. The primary progression-free survival analysis revealed a statistically significant improvement in PFS for the pembrolizumab-chemoradiotherapy arm compared to chemoradiotherapy alone (24-month PFS: 67.8% vs. 57.3%; HR = 0.70; 95% CI, 0.55–0.89; $p = 0.0020$), accompanied by a favorable trend in overall survival [93]. These findings supported regulatory approvals integrating pembrolizumab into primary CCRT for high-risk LACC.

9.3.2. The CALLA Trial

A randomized Phase III trial testing the concurrent addition of the anti-PD-L1 antibody durvalumab to definitive CCRT followed by durvalumab maintenance did not achieve a statistically significant improvement in PFS across its unselected locally advanced population (HR = 0.84; 95% CI, 0.65–1.08; $p = 0.174$) [94]. The discordant outcomes between KEYNOTE-A18 and CALLA underscore the critical importance of patient selection, baseline nodal risk stratification, and specific target engagement (PD-1 versus PD-L1 blockade) when combining checkpoint inhibitors with radiation [94, 95].

10. Antibody-Drug Conjugates (ADCs) and Cellular Immunotherapy

10.1. Antibody-Drug Conjugates: Tisotumab Vedotin (innovaTV 301)

Antibody-drug conjugates (ADCs) deliver cytotoxic payloads to malignant cells by targeting specific surface antigens [96]. Tisotumab vedotin consists of a human monoclonal antibody directed against Tissue Factor (TF)—a transmembrane protein constitutively overexpressed in over 90% of cervical cancers—conjugated via a protease-cleavable valine-citrulline linker to monomethyl auristatin E (MMAE), a potent microtubule-disrupting agent [96, 97]. Upon binding to cell-surface TF, the complex undergoes rapid receptor-mediated endocytosis, trafficking into lysosomes where cathepsin B cleaves the peptide linker, releasing free MMAE into the cytosol to induce G2/M cell cycle arrest and apoptotic cell death [97].

The pivotal Phase III innovaTV 301 trial evaluated tisotumab vedotin versus investigator's choice chemotherapy in patients with recurrent or metastatic cervical cancer who had experienced disease progression on or after doublet chemotherapy with bevacizumab and/or anti-PD-(L)1 therapy [98]. The trial showed:

Overall Survival: Median OS was 11.5 months with tisotumab vedotin versus 9.5 months with conventional single-agent chemotherapy (HR for death = 0.70; 95% CI, 0.54–0.89; $p = 0.0038$) [98].

PFS and Response: Median PFS was extended (HR = 0.67; 95% CI, 0.54–0.82; $p < 0.0001$), with an ORR of 17.8% versus 5.2% [98, 99].

Adverse events associated with tisotumab vedotin include ocular toxicities (conjunctivitis, dry eye keratitis, ulcerative corneal changes) requiring specialized preventive ophthalmic regimens (preservative-free lubricating drops, topical vasoconstrictors, steroid drops, and cooling eye pads), peripheral neuropathy, and bleeding complications [99].

Table 2. Phase III Clinical Trials Evaluating Targeted Therapies, and Immune Checkpoint Inhibitors in Cervical Cancer

Clinical Trial	Study Phase & Design	Study Population	Treatment Arms	Primary Findings & Hazard Ratios
GOG-240 [82]	Phase III Randomized Open-Label	Recurrent, persistent, or metastatic cervical cancer	Chemotherapy doublet ± Bevacizumab (15 mg/kg)	Median OS: 16.8 vs. 13.3 mos HR = 0.77 ($p = 0.007$)
KEYNOTE-826 [87]	Phase III Randomized Double-Blind	First-line persistent, recurrent, or metastatic (PD-L1 CPS ≥ 1)	Chemo ± Bevacizumab ± Pembrolizumab (200 mg)	24-month OS: 53.0% vs. 41.7% HR = 0.64 ($p < 0.001$)
EMPOWER-Cervical 1 [90]	Phase III Randomized Open-Label	Second-line recurrent or metastatic post-platinum failure	Cemiplimab (350 mg) vs. Investigator's Choice Chemo	Median OS: 12.0 vs. 8.5 mos HR = 0.69 ($p < 0.001$)
KEYNOTE-A18 [93]	Phase III Randomized Double-Blind	Locally advanced cervical cancer (FIGO IB2–IIB N+ or III–IVA)	Definitive CCRT ± Pembrolizumab (200 mg)	24-month PFS: 67.8% vs. 57.3% HR = 0.70 ($p = 0.002$)
INTERLACE [80]	Phase III Randomized Open-Label	Locally advanced cervical cancer (FIGO IB1 N+ to IVA)	6 wks weekly carbo/paclitaxel induction →CCRT vs. CCRT	5-year OS: 80% vs. 72% HR = 0.67 ($p = 0.022$)
innovaTV 301 [98]	Phase III Randomized Open-Label	Recurrent/metastatic cervical cancer post 1–2 prior systemic lines	Tisotumab Vedotin vs. Investigator's Choice Chemo	Median OS: 11.5 vs. 9.5 mos HR = 0.70 ($p = 0.0038$)

10.2. Adoptive Cell Therapy with Autologous Tumor-Infiltrating Lymphocytes (TILs)

Adoptive cell transfer using autologous tumor-infiltrating lymphocytes (TILs) represents an emerging option for managing recurrent or metastatic disease [100]. This process involves surgical resection of a tumor deposit, followed by mechanical and enzymatic dissociation to isolate endogenous TILs. These lymphocytes are expanded *ex vivo* using high-dose interleukin-2 (IL-2), screened for specific reactivity against HPV oncoproteins E6 and E7, and expanded to therapeutic volumes [100, 101].

The investigational TIL therapeutic platform LN-145 (Lifileucel platform) has shown reproducible activity in Phase II trials (e.g., C-145-04) [101]. Patients undergo non-myeloablative lymphodepletion chemotherapy (cyclophosphamide and fludarabine) to clear endogenous immunosuppressive regulatory T cells and cytokine sinks, receive a single infusion of autologous LN-145 TILs, and are subsequently treated with brief, high-dose systemic IL-2 to support T-cell proliferation *in vivo* [101, 102].

Clinical trials in advanced, pretreated cervical cancer cohorts have indicated objective response rates exceeding 30% to 40%, with ongoing complete responses observed even after prior platinum, bevacizumab, and anti-PD-1 progression [102]. The primary toxicities associated with TIL therapy derive from transient lymphodepletion-induced myelosuppression and IL-2-related capillary leak syndrome [102, 103].

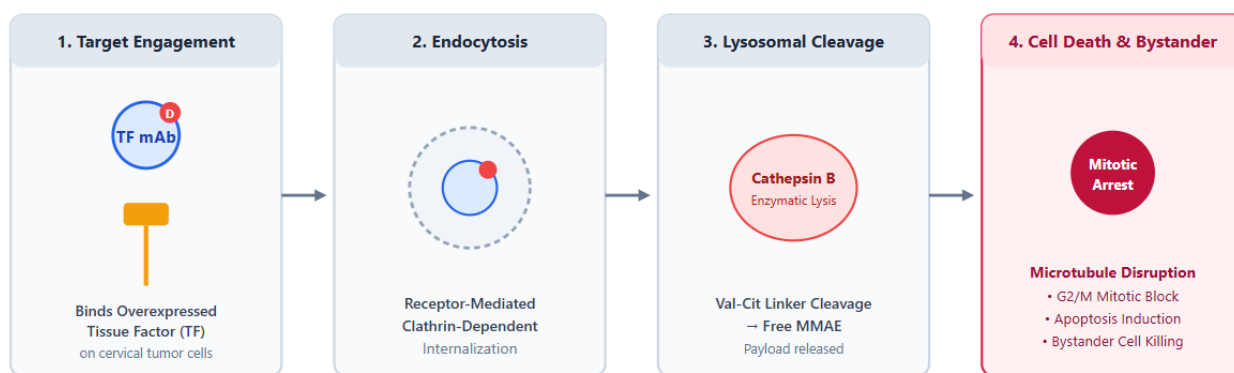


Figure 3. Mechanism of Action of Tisotumab Vedotin (Anti-Tissue Factor ADC)

11. Novel Molecular Targets

11.1. Cell Cycle Checkpoint Regulation

The G2/M cell cycle checkpoint prevents cells with damaged or incompletely replicated DNA from entering mitosis [104]. This checkpoint is regulated by the Wee1 nuclear tyrosine/threonine kinase, which catalyzes inhibitory phosphorylation of CDK1 (Cdc2) at residue Tyrosine-15 (Tyr15), maintaining the cyclin B-CDK1 complex in an inactive state [104, 105]. In non-malignant, healthy tissues, functional p53 acts as the master guardian of the earlier G1/S checkpoint, providing time for DNA repair before replication begins [105]. However, in cervical carcinoma, persistent viral E6-mediated degradation of p53 inactivates the G1/S checkpoint [105, 106]. As a consequence, cervical cancer cells rely heavily on the Wee1-regulated G2/M checkpoint to arrest the cell cycle and repair replication-induced DNA damage before attempting mitosis [106]. Small-molecule Wee1 inhibitors (such as adavosertib / MK-1775) selectively disrupt this process [106, 107]. By blocking Wee1-mediated phosphorylation of CDK1, adavosertib forces p53-deficient cervical cancer cells to bypass G2/M arrest, pushing cells harboring damaged DNA directly into premature, aberrant mitosis [107]. This induces widespread mitotic catastrophe and initiates programmed apoptosis. Early-phase clinical trials investigating adavosertib combined with DNA-damaging agents (carboplatin, cisplatin, or gemcitabine) have shown enhanced radiosensitivity and cytotoxicity in locally advanced and refractory cervical cancers [107, 108].

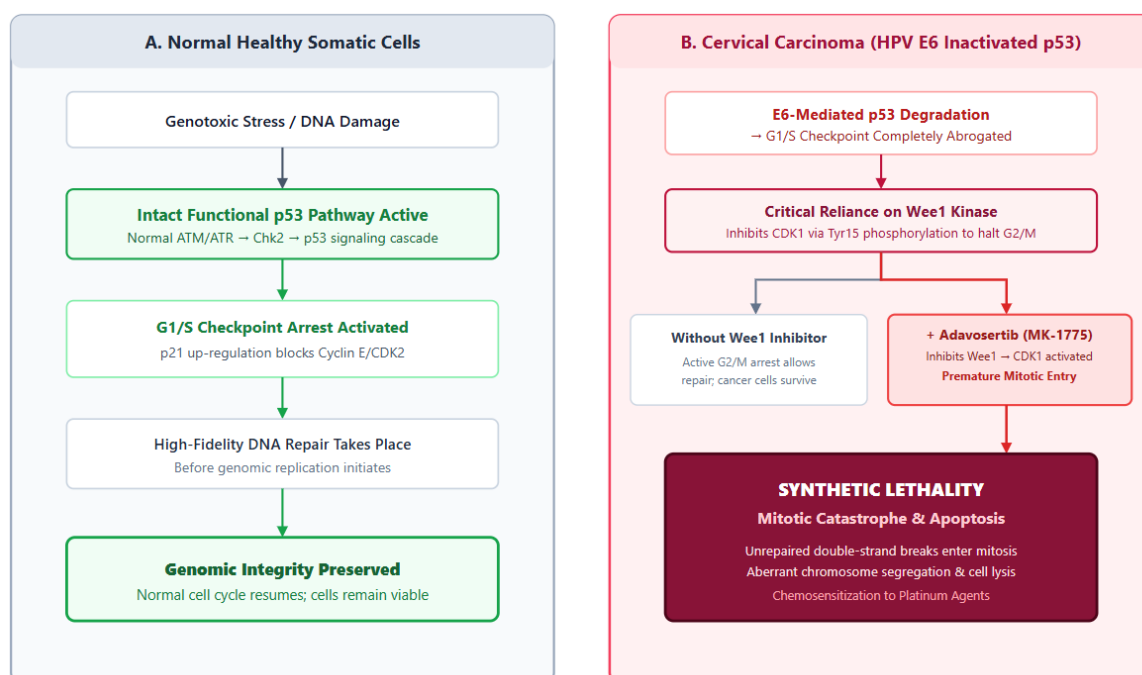


Figure 4. DNA Damage Checkpoint Pathways: Wee1 Synthetic Lethality in p53-Deficient Cervical Cancer

11.2. DNA Damage Repair Vulnerabilities and PARP Inhibition

Poly(ADP-ribose) polymerases (primarily PARP-1 and PARP-2) are nuclear zinc-finger enzymes that detect and repair single-strand DNA breaks (SSBs) through the base excision repair (BER) pathway [108]. When small-molecule PARP inhibitors (e.g., olaparib, rucaparib, niraparib, veliparib) bind to the catalytic domain of PARP, they prevent auto-poly(ADP-ribosylation) and physically trap the inactivated enzyme on damaged DNA [108, 109]. During active S-phase DNA synthesis, advancing replication forks collide with these trapped PARP-DNA complexes, causing replication forks to stall and collapse into cytotoxic double-strand breaks (DSBs) [109].

In normal cells, these replication-induced DSBs are repaired through error-free homologous recombination repair (HRR), a pathway dependent on proteins including BRCA1, BRCA2, RAD51, and PALB2 [110]. In tumors harboring defects in homologous recombination (homologous recombination deficiency, HRD), cell survival pathways are overwhelmed. Unrepaired DSBs are shunted toward error-prone non-homologous end joining (NHEJ), which induces genomic instability, chromosomal rearrangements, and apoptosis—the basis of synthetic lethality [110, 111].

While classic germline *BRCA1/2* mutations are uncommon in cervical cancer, preclinical and translational models show that sustained HPV oncoprotein expression and high baseline levels of reactive oxygen species generate chronic replicative stress and functional HR pathway deficits [111]. High baseline PARP activity is observed in cisplatin-resistant cervical cancer cell lines (such as HeLa derivatives). Combining PARP inhibitors with platinum chemotherapeutics or pelvic ionizing radiation shows promise for sensitizing tumors to DNA damage, and is being evaluated in several ongoing clinical trials [111, 112].

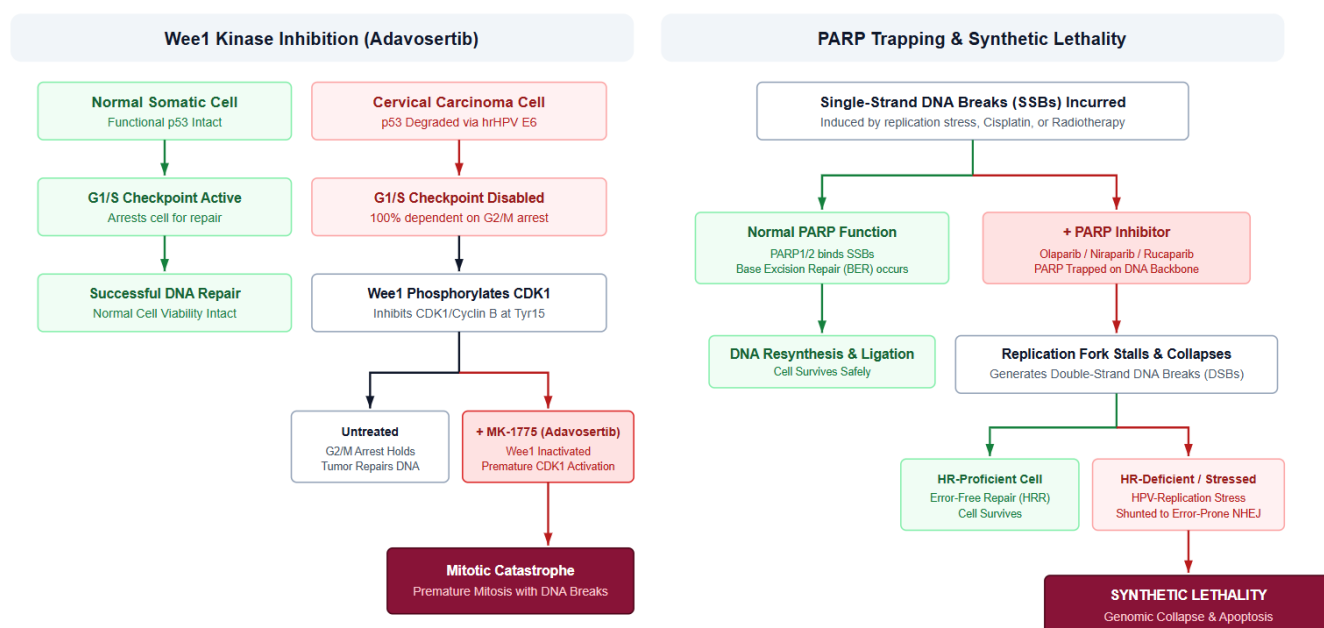


Figure 5. Targeted DNA Damage Response & Synthetic Lethality

11.3. Epidermal Growth Factor Receptor (EGFR) and Downstream Pathways

The epidermal growth factor receptor (EGFR/HER1/ErbB1) is a transmembrane receptor tyrosine kinase overexpressed in approximately 60% to 85% of primary invasive cervical carcinomas, where it correlates with higher recurrence rates, advanced stage, and poor survival [113]. Activation of EGFR by ligands (such as epidermal growth factor or transforming growth factor- α) stimulates downstream cascades, including the MAPK/ERK and PI3K/Akt/mTOR pathways, promoting cell proliferation, motility, and survival [113, 114].

Investigations evaluating early-generation small-molecule EGFR tyrosine kinase inhibitors (gefitinib, erlotinib) or monoclonal antibodies (cetuximab) as monotherapies showed limited objective clinical response rates (< 10%) in unselected cohorts [114]. This lack of monotherapy efficacy is partly explained by activating mutations or amplifications occurring downstream within the catalytic subunit of PI3K (*PIK3CA*), which are present in 20% to 40% of squamous and adenocarcinomatous cervical malignancies [114, 115].

These downstream alterations maintain active intracellular survival signals even when upstream EGFR is successfully blocked. Consequently, contemporary clinical strategies are shifting toward rational combination regimens that simultaneously target multiple nodes along the pathway—combining dual PI3K/mTOR inhibitors, next-generation bispecific antibodies, and antibody-drug conjugates directed at adjacent receptor tyrosine kinase family members [115].

12. Conclusion

The clinical management of cervical carcinoma has shifted from empirical, anatomy-based treatment to refined, biologically driven therapeutic alternatives. At the population level, the global strategy established by the World Health Organization aims to eliminate cervical cancer as a public health concern through the "90-70-90" targets: vaccinating 90% of girls fully against HPV by age 15, screening 70% of women using high-performance molecular assays at ages 35 and 45, and ensuring 90% of identified precancerous and invasive lesions receive timely, high-quality treatment. Meeting these goals requires overcoming socioeconomic disparities and ensuring access to diagnostics and therapeutics across low- and middle-income regions. For localized and locally advanced disease, clinical paradigms prioritize precision. Open radical hysterectomy remains standard for early-stage operable disease, supported by sentinel lymph node ultrastaging to avoid overtreatment. In locally advanced stages, the implementation of three-dimensional MRI-guided adaptive brachytherapy has raised pelvic control rates while sparing surrounding normal tissues, and the integration of dose-dense induction chemotherapy and concurrent immune checkpoint inhibitors shows significant promise in clinical trials. In the persistent, recurrent, and metastatic conditions, survival outcomes have improved through combination regimens incorporating bevacizumab, pembrolizumab, and cemiplimab alongside cytotoxic doublets. The clinical validation of antibody-drug conjugates, such as tisotumab vedotin, and cellular platforms like autologous tumor-infiltrating lymphocytes offers effective therapies for disease that has progressed through prior lines of treatment.

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