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Evolution of Cervical Cancer Radiotherapy: A Case-Based Analysis of Current Staging Systems and Treatment Advances

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ABSTRACT

Cervical cancer remains a significant global health concern, with radiotherapy serving as a cornerstone of treatment for locally advanced disease. Recent advances in imaging technology, treatment planning, and staging systems have revolutionized the management of cervical cancer. This systematic review provides a comprehensive analysis of contemporary cervical cancer radiotherapy approaches, incorporating recent advances in staging systems, biochemical markers, and treatment modalities through case-based analysis. A systematic review of literature published between 2018-2025 was conducted, focusing on radiotherapy advances, staging systems, and biochemical markers in cervical cancer management following PRISMA guidelines. The FIGO 2018 staging system has significantly impacted treatment decisions, with widespread adoption of 3D image-guided brachytherapy and intensity-modulated radiation therapy showing improved outcomes. Tumor markers including SCC-Ag, CEA, and CA125 provide valuable prognostic information for treatment planning and monitoring. Modern cervical cancer radiotherapy has evolved significantly with improved staging accuracy, advanced treatment techniques, and better understanding of biochemical markers leading to personalized treatment approaches. The integration of contemporary staging systems with advanced radiotherapy techniques represents a paradigm shift toward precision oncology in cervical cancer management

Keywords: *cervical cancer; radiotherapy; FIGO staging; tumor markers; IMRT; brachytherapy*

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1. INTRODUCTION

Cervical cancer represents the fourth most common cancer affecting women worldwide, with approximately 570,000 new cases and 311,000 deaths annually [1]. The disease predominantly affects women in developing countries, where access to screening and treatment remains limited. Despite significant advances in prevention through vaccination and screening programs, cervical cancer continues to pose a substantial global health burden.

The evolution of cervical cancer management has been marked by significant milestones, from the initial development of the Papanicolaou smear to the introduction of human papillomavirus (HPV) vaccination. However, for women who develop invasive cervical cancer, treatment outcomes have been dramatically improved through advances in radiotherapy techniques and staging systems.

Historical Context of Cervical Cancer Radiotherapy

Radiotherapy has been a cornerstone of cervical cancer treatment for over a century, with the first successful treatments reported in the early 1900s [2-6]. The traditional approach involved external beam radiation therapy followed by intracavitary brachytherapy, delivering high doses to the tumor while sparing adjacent normal tissues. The development of computed tomography (CT) and magnetic resonance imaging (MRI) in the 1970s and 1980s revolutionized treatment planning and outcome assessment [5].

Recent widespread use of three-dimensional image-guided brachytherapy (3D-IGBT) has improved radiotherapy outcomes of cervical cancer dramatically, marking a new era in precision radiation oncology [6]. The integration of concurrent chemotherapy with radiation therapy, established through landmark clinical trials in the 1990s, further improved survival outcomes and established the current standard of care for locally advanced cervical cancer [4].

2. MATERIALS AND METHODS

Study Design

This systematic review employed a comprehensive case-based analysis approach to evaluate the evolution of cervical cancer radiotherapy, focusing on contemporary staging systems, biochemical markers, and treatment advances. The study was designed as a narrative systematic review with case-based illustrations to demonstrate practical applications of modern cervical cancer management principles.

Literature Search Strategy

A systematic literature search was conducted across multiple electronic databases including PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Google Scholar. The search was limited to peer-reviewed articles published between January 2018 and December 2024 to capture the most recent advances in cervical cancer radiotherapy, particularly following the implementation of the FIGO 2018 staging system.

The search strategy utilized Medical Subject Headings (MeSH) terms and free-text keywords including: "cervical cancer," "uterine cervical neoplasms," "radiotherapy," "radiation therapy," "chemoradiotherapy," "brachytherapy," "FIGO staging," "image-guided radiotherapy," "intensity-modulated radiation therapy," "tumor markers," "SCC-Ag," "CEA," "CA125," "treatment outcomes," and "prognosis." Boolean operators (AND, OR) were used to combine search terms and create comprehensive search strings.

Inclusion and Exclusion Criteria

Inclusion Criteria:

Published in peer-reviewed journals between 2018-2024

Written in English language

Focused on cervical cancer radiotherapy, staging, or biochemical markers

Included original research articles, systematic reviews, meta-analyses, and clinical practice guidelines

Presented data on treatment outcomes, staging accuracy, or biomarker utility

Involved human subjects with histologically confirmed cervical cancer

Reported on contemporary radiotherapy techniques including IMRT, 3D-IGBT, or concurrent chemoradiotherapy

Exclusion Criteria:

Published before 2018 or after December 2024

Focused solely on surgical management without radiotherapy component

Included only preclinical or in vitro studies

Case reports with fewer than 10 patients

Lacked adequate methodological quality or statistical analysis

Conference abstracts, letters to editors, or opinion pieces without original data

Focused on cervical cancer prevention or screening without treatment outcomes

Study Selection Process

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Initial screening involved title and abstract review by two independent reviewers (P.S. and S.T.) to identify potentially relevant studies. Full-text articles were then retrieved for detailed evaluation. Disagreements between reviewers were resolved through consensus discussion or consultation with a third reviewer (B.S.).

Quality assessment was performed using appropriate tools based on study design. For randomized controlled trials, the Cochrane Risk of Bias tool was utilized. For observational studies, the Newcastle-Ottawa Scale was applied. Systematic reviews were evaluated using the AMSTAR-2 tool. Only studies meeting predetermined quality thresholds were included in the final analysis.

Data Extraction and Analysis

Data extraction was performed systematically using a predetermined extraction form including study characteristics, patient demographics, staging methodology, treatment details, biochemical markers, outcome measures, and statistical methods. Representative clinical cases were selected from the literature to illustrate key concepts in contemporary cervical cancer management.

Due to heterogeneity in study designs and outcome measures, formal meta-analysis was not performed. Instead, a narrative synthesis approach was utilized to summarize findings across studies. Subgroup analyses were planned for staging system comparison, radiotherapy technique, disease stage, histological type, and geographic region.

Ethical Considerations

This systematic review utilized previously published data and did not involve direct patient contact or intervention. All included studies had previously obtained appropriate ethical approval from their respective institutional review boards. Patient confidentiality was maintained in all case presentations through de-identification of personal information.

3. RESULTS

Contemporary Staging Systems

FIGO 2018 Staging Classification: Key Updates and Clinical Impact

The International Federation of Gynecology and Obstetrics (FIGO) staging system underwent significant revision in 2018, marking the most substantial change since 1994 [2]. The key modifications include the incorporation of imaging findings and pathological lymph node status, addressing long-standing limitations of the purely clinical staging system [3].

Table 1. FIGO 2018 Staging System for Cervical Cancer

Stage	Description	Key Changes from 2009
IA	Invasive carcinoma diagnosed microscopically	No change
IA1	Stromal invasion ≤3 mm in depth, ≤7 mm horizontal spread	No change
IA2	Stromal invasion >3 mm but ≤5 mm, ≤7 mm horizontal spread	No change

Stage	Description	Key Changes from 2009
IB	Clinically visible lesion or microscopic lesion >IA2	Subdivided into IB1, IB2, IB3
IB1	Clinically visible lesion ≤2 cm	Size criterion changed from 4 cm
IB2	Clinically visible lesion >2 cm but ≤4 cm	New subcategory
IB3	Clinically visible lesion >4 cm	New subcategory
II	Invades beyond uterus but not to lower third of vagina or pelvic wall	No change
IIA	Without parametrial invasion	Subdivided into IIA1, IIA2
IIA1	Clinically visible lesion ≤4 cm	New subcategory
IIA2	Clinically visible lesion >4 cm	New subcategory
IIB	With parametrial invasion	No change
III	Extends to lower third of vagina or pelvic wall	Modified to include lymph nodes
IIIA	Lower third of vagina, no pelvic wall extension	No change
IIIB	Pelvic wall extension or hydronephrosis	No change
IIIC	Pelvic or para-aortic lymph node metastases	**New stage**
IIIC1	Pelvic lymph node metastases	**New subcategory**
IIIC2	Para-aortic lymph node metastases	**New subcategory**
IV	Extends beyond true pelvis or bladder/rectal mucosa	No change
IVA	Bladder or rectal mucosal invasion	No change
IVB	Distant metastases	No change

After revising the FIGO stage in 2018, concurrent chemoradiotherapy (CCRT) was used for stages IB3 to IVA, including new stage IIIC diseases, representing a significant shift in treatment paradigms [4]. The introduction of stage IIIC has been particularly impactful, as it recognizes the prognostic significance of lymph node involvement while maintaining the option for curative-intent treatment [3].

Stage Migration Patterns and Clinical Significance

The implementation of FIGO 2018 staging has resulted in substantial stage migration, with studies reporting upstaging in 47-62% of patients when compared to the 2009 criteria [3]. This stage migration has several important clinical implications including treatment planning with higher stage assignment leading to more aggressive treatment approaches, more accurate prognosis and risk stratification for patient counseling, clinical trial comparisons where historical controls may not be directly comparable, and resource allocation with increased demand for advanced imaging and treatment modalities [4].

Integration of Imaging in Modern Staging

The 2018 FIGO staging system explicitly allows the use of imaging modalities including CT, MRI, and PET-CT for staging purposes (Bhatla et al., 2018)[2]. This represents a paradigm shift from purely clinical assessment to multimodal staging

approaches.

Table 2: Imaging Modalities in Cervical Cancer Staging

Modality	Primary Applications	Advantages	Limitations
MRI	Local tumor assessment, parametrial invasion	Excellent soft tissue contrast, no radiation	Cost, availability, contraindications
CT	Lymph node assessment, distant metastases	Rapid acquisition, widely available	Limited soft tissue contrast
PET-CT	Lymph node assessment, distant metastases	High sensitivity for metastases	False positives, cost
Ultrasound	Initial assessment, guided procedures	Non-invasive, real-time imaging	Operator dependent

Biochemical Investigations and Tumor Markers

Squamous Cell Carcinoma Antigen (SCC-Ag)

Squamous cell carcinoma antigen is a glycoprotein tumor marker derived from the squamous cell carcinoma antigen gene family [7]. SCC-Ag is a member of the serine protease inhibitor (serpin) family, specifically clade B member 3 (SERPINB3) and clade B member 4 (SERPINB4). These proteins are overexpressed in squamous cell carcinomas and play roles in apoptosis inhibition, cell proliferation promotion, angiogenesis stimulation, and immune evasion. Clinical applications include diagnosis, staging, monitoring treatment response, and prognosis assessment.

Carcinoembryonic Antigen (CEA)

Carcinoembryonic antigen is a glycoprotein normally produced during fetal development but can be elevated in various cancers [8]. CEA functions as a cell adhesion molecule facilitating tumor cell aggregation, metastasis promotion, immune suppression, and angiogenesis. It is particularly useful in adenocarcinoma detection, metastasis prediction, and treatment monitoring.

Cancer Antigen 125 (CA125)

CA125 is a high molecular weight glycoprotein that serves as an important tumor marker in gynecological cancers [9]. CA125 contributes to cancer progression through peritoneal implantation, immune evasion, metastasis promotion, and angiogenesis stimulation. Clinical applications include diagnosis, staging, prognosis assessment, and monitoring for recurrence.

Tissue Polypeptide Antigen (TPA)

Tissue polypeptide antigen is a marker of cell proliferation and tissue remodeling [7]. TPS in the 1st, 2nd and 5th compared to the remaining groups showed significant differences [8].TPA is associated with Cell cycle regulation, Tissue remodeling: Indicates active tissue changes, Apoptosis and increased Inflammatory response.

Table 3. Tumor Markers in Cervical Cancer - Reference Values and Clinical Significance

Marker	Normal Range	Elevated in CC	Mechanism	Clinical Use
SCC-Ag	<1.5 ng/mL	>2.0 ng/mL	Protease inhibitor, anti-apoptotic	Squamous cell carcinoma
CEA	<5.0 ng/mL	>10.0 ng/mL	Cell adhesion, metastasis promotion	Adenocarcinoma, metastasis
CA125	<35 U/mL	>65 U/mL	Peritoneal implantation, immune evasion	Advanced disease, monitoring
TPA	<75 U/L	>150 U/L	Cell proliferation marker	Treatment response

External Beam Radiotherapy Innovations

Intensity-Modulated Radiation Therapy (IMRT)

Intensity-modulated radiation therapy (IMRT) and intracavitary brachytherapy with CCRT provided favorable treatment outcomes in cervical cancer patients [10]. IMRT represents a significant advancement over conventional radiotherapy techniques, allowing for precise dose delivery while sparing critical organs [5].

Technical advantages of IMRT include improved conformality with better dose distribution to target volumes, organ sparing with reduced radiation dose to normal tissues, potential for dose escalation with higher tumor doses, and reduced toxicity with lower rates of acute and late complications.

Studies have demonstrated that IMRT compared to conventional radiotherapy results in 40-50% reduction in Grade 3+ gastrointestinal toxicity, 30-40% reduction in genitourinary complications, improved quality of life with better patient-reported outcomes, and similar tumor control with equivalent local control rates [5].

Image-Guided Radiation Therapy (IGRT)

The use of image-guided IMRT (IG-IMRT) and 3D image-guided adaptive brachytherapy (3D-IGABT) have considerably improved treatment outcomes and toxicity profiles for patients with locally advanced cervical cancer (LACC), and are now considered the gold standard in many countries [6]. IGRT incorporates real-time imaging to guide treatment delivery, ensuring accurate dose delivery despite organ motion and setup variations [10].

Brachytherapy Advances

3D Image-Guided Brachytherapy: Current Standards

Three-dimensional image-guided brachytherapy represents the current standard of care for cervical cancer patients receiving definitive radiotherapy [6]. Recent widespread use of 3D-IGBT has improved radiotherapy outcomes of cervical cancer dramatically [10].

Technical innovations include CT-based planning for improved target and organ-at-risk delineation, MRI-guided planning with superior soft tissue contrast, dose-volume optimization for personalized dose distributions, and applicator advances with improved geometry and stability.

Clinical benefits include improved local control with 85-95% local control rates [6], reduced toxicity with lower rates of severe complications [5], better quality of life with preserved organ function [10], and personalized treatment tailored to individual anatomy [6].

High-Dose Rate vs. Low-Dose Rate Brachytherapy

The choice between high-dose rate (HDR) and low-dose rate (LDR) brachytherapy depends on institutional expertise, patient factors, and treatment logistics.

Table 4: Comparison of HDR vs. LDR Brachytherapy

Parameter	HDR Brachytherapy	LDR Brachytherapy
Treatment duration	10-20 minutes	48-72 hours
Hospitalization	Outpatient	Inpatient
Optimization	Real-time possible	Limited
Radiation protection	Minimal exposure	Strict precautions
Cost	Lower overall	Higher overall
Patient comfort	Better	Requires immobilization
Efficacy	Equivalent	Equivalent

Case-Based Analysis

Table 5. Cervical Cancer Case-Based Analysis: Comparative Summary [11-21]

Parameter	Case 1: Early-Stage with Fertility Preservation	Case 2: Locally Advanced with CRT	Case 3: Recurrent Disease Management
Patient Profile			
Age	28 years old	45 years old	52 years old
Histology	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma
Stage	IB1	IIIC1	Recurrent (previous CRT)
Tumor Size/Disease Extent	1.8 cm	Bulky parametrial disease	Central recurrence
Nodal Status	Not specified	Positive pelvic lymph nodes on imaging	No distant metastases
Primary Concern	Fertility preservation	Advanced disease management	Salvage treatment
Time to Recurrence	N/A	N/A	18 months post-treatment
Biochemical Markers			
SCC-Ag	2.8 ng/mL (elevated)	12.4 ng/mL (significantly elevated)	8.9 ng/mL (elevated)
CEA	3.2 ng/mL (normal)	8.7 ng/mL (elevated)	15.3 ng/mL (elevated)
CA125	28 U/mL (normal)	85 U/mL (elevated)	125 U/mL (elevated)
Treatment Approach			
Primary Treatment	Radical trachelectomy with pelvic lymphadenectomy	External beam radiotherapy (45 Gy/25 fractions)	Pelvic exenteration
Secondary Treatment	Radiotherapy deferred based on pathology	Concurrent cisplatin chemotherapy	Reconstruction with intestinal conduit
Additional Treatment	Fertility counseling and follow-up	3D image-guided brachytherapy boost	Adjuvant chemotherapy
PATHOLOGICAL/SURGICAL RESULTS			
Surgical Margins	Negative	N/A	Clear margins achieved
Lymph Node Status	Negative	N/A	N/A

Parameter	Case 1: Early-Stage with Fertility Preservation	Case 2: Locally Advanced with CRT	Case 3: Recurrent Disease Management
CLINICAL OUTCOMES			
Early Response (3-6 months)	Not specified	Complete clinical response at 3 months	Tumor markers normalized
Intermediate Response (6-18 months)	Successful pregnancy at 18 months	Tumor markers normalized within 6 months	No evidence of recurrence at 18 months
Long-term Response (2+ years)	No evidence of recurrence at 3 years	No evidence of recurrence at 2 years	Follow-up ongoing
Complications/Toxicity	None reported	Grade 2 late bowel toxicity	Significant quality of life impact
KEY LEARNING POINTS			
Point 1	Fertility preservation possible in carefully selected early-stage patients	Elevated tumor markers correlate with advanced disease	Salvage surgery remains best option for central recurrence
Point 2	Normal tumor markers support conservative approach	Concurrent chemoradiotherapy remains standard of care	Tumor markers useful for monitoring response
Point 3	Multidisciplinary team approach is essential	3D-IGBT improves outcomes with acceptable toxicity	Quality of life considerations are paramount

4. DISCUSSION

The evolution of cervical cancer radiotherapy has been marked by significant advances across multiple domains [5]. The introduction of the FIGO 2018 staging system has fundamentally improved prognostic accuracy and treatment selection by incorporating imaging findings and nodal assessment into the staging framework [2]. This enhanced staging approach has enabled more precise risk stratification and treatment planning, leading to better clinical outcomes.

Technical advances in radiotherapy delivery, particularly the widespread adoption of intensity-modulated radiation therapy (IMRT) and three-dimensional image-guided brachytherapy (3D-IGBT), have become the standard of care with demonstrably improved outcomes and reduced toxicity profiles compared to conventional techniques [6].

The integration of biomarkers, particularly tumor markers such as SCC-Ag, CEA, and CA125, has provided valuable prognostic and monitoring information that complements imaging studies and clinical assessment [9]. These biochemical markers have proven particularly useful in treatment response evaluation and long-term surveillance, enabling more personalized treatment approaches.

Emerging Treatment Paradigms

The integration of immunotherapy into cervical cancer treatment represents a promising frontier. Recent clinical trials have demonstrated the efficacy of immune checkpoint inhibitors in recurrent and metastatic disease, with mechanisms including PD-1/PD-L1 inhibition using pembrolizumab and nivolumab, CTLA-4 inhibition with ipilimumab, and combination approaches with chemotherapy plus immunotherapy.

Understanding of cervical cancer molecular biology has led to targeted therapeutic approaches including VEGF inhibition with bevacizumab (FDA approved), EGFR inhibition with cetuximab (investigational), and various pathway inhibitions currently under investigation.

Quality of Life and Toxicity Management

Modern radiotherapy techniques have significantly reduced toxicity rates while maintaining excellent tumor control [5]. The use of IG-IMRT and 3D-IGABT have considerably improved treatment outcomes and toxicity profiles for patients with LACC [6]. Modern techniques focus on dose constraints for critical organs including bladder (V65 <50%, V40 <100%), rectum (V60 <50%, V40 <100%), bowel (V45 <200 cc, V30 <500 cc), and kidneys (mean dose <18 Gy).

Artificial Intelligence in Treatment Planning

The integration of artificial intelligence (AI) and machine learning in cervical cancer treatment planning represents a rapidly evolving field [6]:

Current Applications includes Auto-contouring by Automated organ delineation, Treatment planning based on Dose optimization algorithms, Quality assurance by Plan review and verification and also Outcome prediction Prognostic modelling.

Future Possibilities: the future possibilities are as follows

- Radiomics: Imaging biomarker extraction
- Adaptive therapy: Real-time plan modification
- Predictive modeling: Personalized treatment selection
- Toxicity prediction: Risk assessment tools

Biomarker-Guided Therapy Selection

The future of cervical cancer treatment lies in personalized medicine approaches [9]:

Emerging Biomarkers: These are the emerging biomarkers that may guide the treatment of cervical cancer.

- HPV genotyping: Treatment response prediction
- Tumor mutational burden: Immunotherapy selection
- Microsatellite instability: Targeted therapy options
- Circulating tumor DNA: Minimal residual disease detection

5. CONCLUSIONS

Modern cervical cancer radiotherapy has evolved significantly with improved staging accuracy through the FIGO 2018 system, advanced treatment techniques including IMRT and 3D-IGBT, and better understanding of biochemical markers leading to personalized treatment approaches. The integration of contemporary staging systems with advanced radiotherapy techniques represents a paradigm shift toward precision oncology in cervical cancer management.

Based on current evidence, clinical practice recommendations include utilizing FIGO 2018 staging criteria with full imaging integration, routine incorporation of tumor markers in baseline assessment, employing IMRT for external beam radiotherapy delivery, and utilizing 3D image-guided brachytherapy whenever possible. Future research priorities should focus on precision medicine development, combination therapy optimization, quality of life research, and global health considerations to improve access to advanced techniques in resource-limited settings.

Future Research Priorities

To continue improving cervical cancer outcomes, future research efforts should focus on several key areas that will advance the field toward more effective and personalized treatment approaches. Precision medicine represents a critical frontier, with the development of comprehensive molecular profiling for treatment selection holding significant promise. This approach would enable clinicians to select optimal therapies based on individual tumor characteristics, potentially improving outcomes while minimizing unnecessary toxicity. The integration of genomic, proteomic, and metabolomic analyses could identify novel therapeutic targets and predictive biomarkers that guide treatment decisions.

Combination therapies represent another crucial area of investigation, particularly the optimal integration of immunotherapy and targeted agents with conventional treatment modalities. Understanding the synergistic effects of these combinations, determining optimal sequencing, and identifying patient populations most likely to benefit will be essential for maximizing therapeutic benefit. Quality of life research focusing on long-term survivorship and functional outcomes is increasingly important as survival rates improve, ensuring that patients not only survive their cancer but maintain acceptable quality of life throughout their survivorship journey.

Global health considerations remain paramount, with efforts needed to improve access to advanced techniques in resource-limited settings where the burden of cervical cancer is highest. This includes developing cost-effective treatment protocols, training programs for healthcare providers, and infrastructure development to support modern radiotherapy techniques.

Finally, continued efforts in prevention through HPV vaccination and screening programs represent the most effective long-term strategy for reducing cervical cancer incidence and mortality globally, requiring sustained public health initiatives and international cooperation to achieve maximum impact.

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