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COMPLICATIONS OF LOCALLY ADVANCED CERVICAL CANCER AFTER COMPLEX TREATMENT.

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Abstract:

Locally advanced cervical cancer (LACC) remains a significant clinical problem worldwide, especially in low- and middle-income countries. Standard complex treatment involves chemoradiation therapy with or without surgical intervention. Despite advances in multimodal management, patients often experience early and late complications that affect quality of life and long-term survival. This article analyzes the types, frequency, and risk factors of complications following complex treatment of LACC, with particular attention to urogenital, gastrointestinal, hematologic, and psychosocial consequences. Evidence from clinical studies and recent literature is discussed, and recommendations for reducing treatment-related morbidity are presented.

Keywords: Cervical cancer; locally advanced; complications; chemoradiotherapy; radiotherapy toxicity; quality of life; oncological outcomes.

Cervical cancer is one of the most common malignancies among women worldwide, with locally advanced stages (FIGO IIB–IVA) accounting for a substantial proportion of diagnoses. Advances in screening and vaccination have reduced incidence in developed countries, yet in many regions it remains a leading cause of cancer-related death.

The cornerstone of treatment for LACC is concurrent chemoradiotherapy (CRT), often followed by brachytherapy and, in select cases, surgery. While these approaches improve survival, they are associated with a range of acute and chronic complications. Understanding these complications is critical for optimizing patient management, improving survivorship, and guiding future therapeutic strategies.

Locally advanced cervical cancer (LACC), typically encompassing International Federation of Gynecology and Obstetrics (FIGO) stages IB3 to IVA, is primarily treated with complex multimodal approaches. The standard of care is concurrent chemoradiotherapy (CCRT), which combines platinum-based chemotherapy (e.g., cisplatin) with external beam radiotherapy (EBRT) and brachytherapy. In select cases, neoadjuvant chemotherapy (NACT) may precede definitive treatment, or completion surgery (e.g., radical hysterectomy) may follow CCRT. While these regimens improve survival rates—achieving 5-year overall survival (OS) of approximately 60-80%—they are associated with significant acute and late complications. Acute toxicities occur during or shortly after treatment and are often reversible, whereas late toxicities can manifest months to years later, potentially becoming chronic and impacting quality of life (QoL). Factors influencing complication rates include radiation dose, chemotherapy intensity, patient comorbidities (e.g., age, smoking, diabetes), tumor size, and treatment technique (e.g., intensity-modulated radiotherapy reduces risks compared to older methods). Overall, severe (grade 3-4) acute toxicities affect 20-40% of patients, while late severe morbidities occur in 10-20%, with no significant increase from adding chemotherapy to radiotherapy alone. Modern image-guided adaptive brachytherapy (IGABT) has reduced severe late morbidity to around 5-10% at 5 years.

Acute Complications

Acute toxicities, graded using systems like the Common Terminology Criteria for Adverse Events (CTCAE), predominantly stem from chemotherapy's systemic effects and radiation's impact on pelvic organs. They typically peak during weeks 3-5 of treatment and resolve within 3 months. CCRT increases acute hematological and gastrointestinal (GI) toxicities compared to radiotherapy alone, but rates of severe events remain manageable with supportive care (e.g., antiemetics, growth factors). Feasibility studies confirm CCRT's tolerability, with completion rates exceeding 90%.

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The following table summarizes common acute complications, their incidence, and management:

Category	Specific Complications	Incidence (Overall / Grade 3-4)	Notes and Management
Hematological	Leukopenia, anemia, thrombocytopenia, neutropenia	30-60% / 10-30%	More common with cisplatin; managed with transfusions, growth factors (e.g., G-CSF). Neutropenia in 32% during NACT.
Gastrointestinal	Diarrhea, nausea, vomiting, proctitis	40-70% / 5-20%	Diarrhea in up to 70%; antiemetics (e.g., ondansetron) and hydration key.
Genitourinary	Cystitis, dysuria, urinary frequency/infections	20-40% / 5-10%	Hydration and urinary alkalinization reduce cisplatin nephrotoxicity.
Dermatological/Mucosal	Dermatitis, mucositis, vaginal irritation	10-30% / <5%	Topical agents and hygiene; rare severe cases.
Other	Fatigue, ototoxicity, neurotoxicity	50-80% / <10%	Cisplatin-specific; dose adjustments prevent progression.

Adding hyperthermia to CCRT does not significantly increase acute toxicities. Prolonged treatment time (>7-9 weeks) exacerbates acute effects and worsens outcomes.

Late Complications

Late toxicities result from radiation-induced fibrosis, ischemia, and inflammation, often irreversible and progressive. They affect QoL, with persistent symptoms in up to 30% of survivors. Severe late morbidity (grade ≥3) occurs in 5-15% overall, with GI and genitourinary (GU) systems most impacted. CCRT does not substantially elevate late risks compared to radiotherapy alone, but higher doses correlate with increased incidence.

Key late complications include:

Category	Specific Complications	Incidence (Overall / Grade 3-4)	Notes and Management
Gastrointestinal	Chronic proctitis, rectal bleeding, diarrhea, bowel obstruction, fistulas (e.g., rectovaginal), stenosis	10-30% / 5-10%	Bleeding in 5-10%; hyperbaric oxygen or surgery for severe cases. Bowel issues require surgery in 1-5%.
Genitourinary	Chronic cystitis, hematuria, ureteral stricture, bladder fibrosis, incontinence	5-20% / 3-8%	Bladder complications in 6-14%; cystoscopy or stenting needed.
Sexual/Reproductive	Vaginal stenosis, dryness, dyspareunia, loss of libido, infertility	20-50% / 10-20%	Dilators and lubricants; hormone therapy for menopause.
Skeletal/Vascular	Bone fractures (e.g., pelvic), vascular damage, lymphedema	5-15% / <5%	Osteoporosis risk; bisphosphonates or physical therapy.
Other	Secondary malignancies, chronic fatigue, QoL reduction	1-5% / Variable	Long-term surveillance; multidisciplinary support.

Predictive factors for late toxicity include rectal/bladder doses >70-75 Gy, large tumor volume, and smoking.

Complications Specific to Additional Modalities

- Neoadjuvant Chemotherapy (NACT): Used to downstage tumors before surgery or CCRT, NACT (e.g., cisplatin-paclitaxel) adds hematological toxicities like grade 3-4 neutropenia (29-32%) and anemia, but reduces radiation volumes potentially lowering late GI/GU risks. However, meta-analyses show similar survival to CCRT but with higher acute toxicity in some regimens. NACT followed by surgery has lower late toxicity than CCRT but similar OS.
- Completion Surgery after CCRT: Performed for residual disease, it increases morbidity (e.g., urinary/bowel issues in 10-20%, fistulas in 5%) and does not improve OS, potentially worsening late effects. Guidelines recommend against routine use due to added risks.

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In recurrent cases, re-treatment intensifies complications, requiring individualized approaches. Ongoing research focuses on minimizing toxicities through advanced techniques like proton therapy.

The findings confirm that although complex treatment improves survival in LACC, complications remain a substantial burden. Advanced radiotherapy techniques and supportive interventions reduce but do not eliminate long-term morbidity. Risk factors for severe complications include higher radiation doses, poor nutritional status, comorbidities, and limited access to follow-up care.

Efforts to minimize complications include:

Use of intensity-modulated radiotherapy (IMRT) and image-guided brachytherapy.

Introduction of protective agents (e.g., amifostine) in selected cases.

Early rehabilitation programs addressing sexual health, pelvic floor dysfunction, and psychosocial adaptation.

Regular follow-up with multidisciplinary teams for early detection and management of complications.

CONCLUSIONS

Complex treatment of LACC significantly improves survival but leads to both acute and chronic complications. Urological, gastrointestinal, and sexual health complications are most common and can severely impair quality of life. Adoption of advanced radiotherapy techniques and supportive care reduces complication rates. Multidisciplinary follow-up care, including gynecologic oncologists, radiation oncologists, psychologists, and rehabilitation specialists, is essential. Future research should focus on biomarkers predicting toxicity, patient-centered survivorship programs, and broader access to modern radiotherapy technologies.

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