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Failure Patterns and Prognostic Factors in Stage IIIC Cervical Squamous Cell Carcinoma Treated with Definitive Radiotherapy: A Retrospective Study

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Abstract

Background

Cervical squamous cell carcinoma remains a global health burden, often diagnosed at advanced stages. Stage IIIC disease (2018 FIGO) presents significant patient heterogeneity. This study focuses on this high-risk subgroup, aiming to delineate treatment failure patterns following comprehensive therapy and identify independent prognostic factors for survival outcomes.

Methods

This single-center retrospective study included 211 stage IIIC cervical squamous cell carcinoma patients treated definitively (2017–2023). Treatment failure patterns (local recurrence, distant lymph node metastasis, hematogenous metastasis) were defined by imaging/pathology. Overall survival and progression-free survival were analyzed using Kaplan-Meier with Log-rank tests. Prognostic factors were assessed via Chi-squared test, Kaplan-Meier, Log-rank, and Cox regression.

Results

The recurrence rate was 19.4% (41/211) over a median follow-up of 25 months. Distant metastasis was the predominant failure pattern (80.5%), with the lungs being the most common site of hematogenous spread (46.3%). Multivariate analysis identified a pre-treatment squamous cell carcinoma antigen level ≥ 4.1 ng/mL (P = 0.010) and a progression-free survival of ≤ 18.55 months (P = 0.002) as independent predictors of poorer overall survival.

Conclusion

For stage IIIC CSCC, distant metastasis is the primary pattern of treatment failure. Pre-treatment SCC-Ag and early disease progression are robust independent prognostic factors, offering critical insights for risk-adapted treatment strategies.

1. Background

Cervical squamous cell carcinoma (CSCC) remains a major global health threat to women, especially in regions with inadequate screening, and is characterized by high incidence and a poor prognosis in advanced stages[1, 2]. This is particularly true for stage IIIC disease, which encompasses a heterogeneous patient population with widely varying tumor burdens and metastatic patterns, further complicating prognosis and treatment planning[3, 4]

Lymphatic metastasis is one of the most important and earliest pathways of metastasis, and its incidence and extent are directly correlated with clinical staging. The FIGO 2018 staging system for the first time Incorporated lymph node metastasis status into the formal staging (starting from Stage IIIC), highlighting the importance of lymph node metastasis in cervical cancer while overlooking tumor size, extent of tumor spread, number of lymph nodes, and other factors[5–7]. Among patients with stage IIIC1 disease, local tumor-related factors (such as T stage) are significantly associated with survival rates, with 5-year survival rates being 74.8% for T1, 58.7% for T2, and 39.3% for T3[8]. In patients with stage IIICp cervical cancer undergoing radical surgery, the number of positive lymph nodes is closely related to survival[9, 10]. Further studies have shown that recurrence and metastasis in stage IIIC1 are associated with T stage, the extent of pelvic lymph node metastasis[7, 11, 12], lymph node diameter[12], and the number of lymph node metastases. Due to the significant heterogeneity in survival prognosis among patients with stage IIIC cervical cancer and the lack of a unified standard for related prognostic stratification, the recommended standard treatment for stage IIIC cervical cancer across guidelines remains concurrent chemoradiotherapy[13]. Despite this established regimen, treatment outcomes remain suboptimal, with 30–50% of patients experiencing treatment failure in the form of locoregional recurrence or distant metastasis[14, 15]. This high rate of failure underscores the urgent need for reliable tools to identify high-risk patients before treatment intensification.

However, a unified standard for prognostic stratification in CC is currently lacking[16]. Therefore, investigating the failure patterns and associated risk factors in post-treatment of stage III C cervical cancer patients will facilitate the development of more individualized treatment strategies, providing clinical evidence to reduce recurrence or metastasis, improve patient prognosis, and enhance quality of life.

Pre-treatment tumor markers such as squamous cell carcinoma antigen (SCC-Ag), are closely associated with patient prognosis[17]. In stage IIIC CSCC, elevated SCC-Ag levels may reflect greater tumor burden, aggressive biology, and treatment response[18], and its dynamics are used to monitor therapy and detect recurrence[19]. Tumor stage, lymph node status, surgical margin status, and lymphovascular space invasion are also significantly correlated with the prognosis of cervical cancer patients[20, 21]. Moreover, emerging evidence suggests that a combination of molecular profiles, tumor volume, and imaging characteristics could refine risk assessment[22, 23].

Nevertheless, most studies incorporating such markers have only focused on early-stage patients or to cohorts encompassing all stages, and systematic analyses dedicated to the distinct failure patterns and multifactorial prognosis specifically in stage IIIC patients are scarce. This gap contributes to the lack of effective predictive tools in clinical practice.

Therefore, this retrospective study aimed to systematically characterize the patterns of treatment failure, and identify comprehensive prognostic factors in a defined cohort of patients with stage IIIC CSCC

treated with definitive radiotherapy. The findings are expected to enhance risk stratification and inform clinical decision-making for this high-risk population.

2. Methods

2.1 Study Population

This retrospective study included 243 patients with histologically confirmed stage IIIC CSCC who received treatment between January 2017 and September 2023.

The inclusion criteria were as follows: (1) Pathologically confirmed diagnosis of squamous cell carcinoma; (2) FIGO 2018 stage IIIC disease, with pelvic/para-aortic lymph node metastasis (IIIC1r/p or IIIC2r/p) confirmed by imaging or pathological examination (i.e., radical surgery or lymph node sampling); (3) Availability of pre-treatment pelvic magnetic resonance imaging (MRI) and chest/abdominal computed tomography (CT) or whole-body positron emission tomography-CT (PET/CT) within 2 weeks for staging; (4) Receipt of initial definitive treatment defined as either definitive concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy, or radical surgery followed by postoperative chemoradiotherapy with or without adjuvant chemotherapy; (5) a ECOG score ≤ 1; (6) Adequate cardiopulmonary, hepatic, and renal functions with no contraindications to radiotherapy or chemotherapy; (7) Absence of distant metastasis (M1 disease) at initial diagnosis and during the primary treatment course; (8) No history of other concurrent malignancies; (9) Complete clinicopathological and follow-up data.

Based on these criteria, 32 patients were excluded: 13 due to failure to complete radiotherapy (external beam or intracavitary brachytherapy) or scheduled cycles of chemotherapy, and 19 lost to follow-up. Thus, the final study cohort comprised 211 eligible patients. From this cohort, 41 patients who experienced recurrence or metastasis were identified for further analysis (Fig. 1).

The study protocol was approved by the hospital's Ethics Committee (Approval Number: 2025-E1033) and conformed to the tenets of the Declaration of Helsinki.

2.2 Diagnostic Criteria for Lymph Node Metastasis

The diagnostic assessment for lymph node metastasis integrated imaging criteria and definitive histopathological findings.

For imaging evaluation, lymph nodes were considered suspicious on CT if meeting any of the following criteria: a short-axis diameter ≥ 10 mm, the presence of central necrosis, or grouping (clustering) of multiple lymph nodes[24]. Magnetic resonance imaging (MRI) evaluation, primarily based on T2-weighted images, defined a node as positive if exhibiting one or more of: (1) a short-axis diameter ≥ 10 mm; (2) central necrosis[25, 26]; or (3) extracapsular extension, characterized by irregular or spiculated margins

with infiltration into the perinodal fat[24]. On ^{18}F-FDG PET/CT, a lymph node was considered positive if its maximum standardized uptake value (SUVmax) was ≥ 2.5[27].

The definitive diagnosis of lymph node metastasis (corresponding to FIGO 2018 stages IIIC1p and IIIC2p) was established by histopathological examination of specimens obtained from radical hysterectomy with pelvic/para-aortic lymphadenectomy or lymph node sampling. This approach is consistent with the FIGO 2018 staging system, which requires pathological confirmation for the “p” designation in surgical cases.

2.3 Treatment Protocols

2.3.1 Radiotherapy

External beam radiotherapy was delivered via intensity-modulated radiation therapy (IMRT) at a dose of 45–50 Gy in 25 fractions, 1.8-2.0 Gy per fraction, 5 fractions per week. For patients with para-aortic lymph node metastasis, extended field radiation therapy (EFRT) was administered up to the renal vessel level, with a simultaneous integrated boost of 5–15 Gy delivered to positive or enlarged lymph nodes. A parametrial boost of 10–15 Gy was selectively added for cases with parametrial or pelvic sidewall invasion. Intracavitary brachytherapy delivered 28–30 Gy to point A in 5 fractions of 6 Gy or 4 fractions of 7 Gy, with the complete radiotherapy course finished within 8 weeks. For patients who underwent radical surgery, the postoperative regimen consisted of concurrent chemoradiotherapy with IMRT. The prescribed doses were 45–50 Gy in 25 fractions to the clinical/high-risk target volume. Dose constraints for organs at risk were as follows: femoral heads V30 < 15%; bone marrow V10 < 80% and V20 < 66%; bladder V45 < 50%; spinal cord ≤ 45 Gy; rectum V45 < 50%; kidneys Dmean < 10Gy.; small bowel V40 < 30%.

2.3.2 Chemotherapy

Concurrent chemotherapy consisted of cisplatin at 40 mg/m² weekly for 5–6 cycles or 100 mg/m² every 3 weeks for 2 cycles, carboplatin at 2 AUC weekly for 5–6 cycles, or lobaplatin at 50 mg/m² every 3 weeks for 2 cycles. Adjuvant chemotherapy, comprising 2–3 cycles repeated every 3 weeks, utilized cisplatin at 80–100 mg/m² on day 1 combined with either docetaxel at 75 mg/m², albumin-bound paclitaxel at 75 mg/m², or 5-fluorouracil at 500 mg/m² on days 1–5. Supportive care including hydration, antiemetics, and hepatoprotective and gastroprotective agents was provided during chemotherapy.

2.3.3 Surgery

Surgical procedures included radical hysterectomy, resecting the uterus, adnexa, vagina, parametrial tissues, and lymph nodes. Lymph node sampling for staging involved pelvic lymph node dissection with or without para-aortic lymph node dissection. A sentinel lymph node (SLN)-guided strategy was applied where systematic dissection was omitted for bilateral negative SLNs, performed for positive SLNs, and mandatory on the non-mapping side for unilateral non-visualization. All radiologically suspicious lymph nodes with a short-axis diameter ≥ 1 cm or signs of necrosis were resected.

2.4 Follow-up and Outcomes

2.4.1 Follow-up

Patients were followed from the initiation of treatment until January 30, 2025. Follow-up encompassed both standardized evaluations and study-specific data collection. The standardized assessments, aligned with the FIGO 2018 schedule (every 3 months for years 1–2, every 6 months for years 3–5, and annually thereafter), included physical and pelvic examinations, cervical cytology, and imaging (pelvic MRI/CT with or without PET-CT).

2.4.2 Definition of Failure Patterns

Locoregional recurrence was defined as recurrence within the radiotherapy field, categorized as central recurrence involving the cervix, parametria, or vagina, or as nodal recurrence in pelvic or irradiated para-aortic lymph nodes. Distant metastasis referred to recurrence outside the radiotherapy field, categorized as distant nodal metastasis such as in supraclavicular or hematogenous metastasis to organs, peritoneum, or bones. Clinical confirmation of failure required histopathological proof from the recurrence site; when a biopsy was unavailable, diagnosis was based on characteristic symptoms, positive signs, and imaging evidence from CT, MRI, or PET/CT.

2.4.3 Study Endpoints

Overall Survival (OS) was defined as the time from diagnosis to death or the last follow-up by the cut-off date. Progression-Free Survival (PFS) was defined as the time from diagnosis to progression or death. The optimal cut-off value was determined by receiver operating characteristic (ROC) curve analysis. The threshold that maximized the Youden index (sensitivity + specificity − 1) was selected as the optimal cut-point[28]. All event endpoints were recorded per RECIST 1.1 criteria.

2.5 Statistical Analysis

Statistical analysis was performed using SPSS 25.0. Survival analysis was performed using the Kaplan-Meier method, with between-group comparisons assessed by the log-rank test. Variables with $P < 0.1$ in univariate analysis, along with those considered clinically important based on a priori knowledge, were entered into a multivariate Cox proportional hazards regression model to identify independent prognostic factors. Statistical significance in the final model was defined as a two-sided P-value < 0.05.

3. Results

3.1 Baseline Clinicopathological Characteristics of the Study Cohort

At the follow-up cutoff date of January 30, 2025, a total of 211 patients were included, with a median follow-up of 23 months. Of these, 41 patients (19.4%) developed recurrence or metastasis. This

treatment failure cohort comprised 29 patients (70.7%) who had received primary radical concurrent chemoradiotherapy (CCRT), with or without adjuvant chemotherapy, and 12 (29.3%) who had undergone radical surgery followed by adjuvant chemoradiotherapy. Regarding the failure patterns, locoregional recurrence only was observed in 8 patients (19.5%), distant metastasis only in 27 (65.9%), and combined locoregional and distant metastasis in 6 (14.6%). Pathological confirmation of lymph node metastasis was obtained in 15 patients (36.6%), with the other 26 (63.4%) being diagnosed based on clinical and radiological criteria. The detailed clinicopathological characteristics of this cohort are summarized in Supplemental Table 1.

3.2 Patterns of Treatment Failure

Distant metastasis was the dominant failure pattern, occurring in 33 (80.5%) of the 41 patients (Fig. 2). The distribution of distant metastases encompassed the lung (19, 46.3%), distant lymph nodes (8, 19.5%), bone (5, 12.2%), and liver (4, 9.8%), with rare involvement of the kidney, brain, and pleura (Supplemental Table 2). Locoregional failures occurred in 14 patients, one of whom had concurrent central and regional nodal recurrence. Among 14 patients, 8 had only locoregional failure and other 6 had concurrent distant metastases. Of 8 patients with distant lymph node metastasis, five had involvement of both supraclavicular and cervical regions, while two had involvement of supraclavicular, mediastinal, and cervical regions.

3.3 Survival Outcomes of Patients with Treatment Failure

With a median follow-up of 25 months (range, 3.85–91.99) for the entire cohort, the median time to recurrence or metastatic was 16 months (range, 1.94–52.13), the median post-recurrence survival was 10.09 months (range, 0-72.3), the median PFS was 16 months (range, 1.94–52.13), and the median OS was 36.90 months (range, 3.85–91.99). The median OS was 19.03 months for patients with lung metastases and 47.78 months for those without, although this difference was not statistically significant (P = 0.307) (Supplemental Table 3). The median OS did not differ significantly between patients with and without bone metastasis (36.90 vs 35.20 months, P = 0.347), liver metastasis (36.90 vs 35.20 months, P = 0.916), hematogenous metastasis (23.57 vs 41.79 months, P = 0.158) (Supplemental Table 3).

3.4 ROC Curve Analysis

The ROC curve showed that the best threshold for predicting prognosis using SCCA was 4.1, the area under the curve was 0.644 (95% CI: 0.461–0.826), the sensitivity was 0.885, and the 1 − specificity was 0.533. The best cut-off value of PFS for predicting prognosis after treatment was 18.55, the area under the curve was 0.550 (95% CI: 0.354–0.746), the sensitivity was 0.808, and the 1 − specificity was 0.533. Combined with the optimal cut-off values and clinical practice, SCCA was divided into < 4.1 and ≥ 4.1, and PFS was divided into ≤ 18.55 and > 18.55.

3.5 Risk Factors for OS in Patients with Treatment Failure

Univariate analysis revealed that Pretreatment SCC-Ag (P = 0.030, and Progression-Free Survival (P = 0.007) were associated with OS. In the multivariate Cox analysis, both factors retained independent significance: PFS status (HR, 5.339; 95% CI, 1.812–16.088; P = 0.002) and, more strongly, Pretreatment SCC-Ag (HR, 0.185; 95% CI, 0.051–0.665; P = 0.010). The detailed results are presented in Table 1.

Table 1
Single-factor and multi-factor analysis of OS influencing factors in cervical cancer patients who fail after treatment

Basic Characteristics	**Univariable Cox analysis**		**Multivariate Cox analysis**	
	n (%)	***p***	**HR (95%)**	***p***
Age (years)		0.655		
> 50	27 (65.9%)			
≤ 50	14 (34.1%)			
FIGO Stage (2018)		0.539		
C1	33 (80.4%)			
C2	8 (19.6%)			
Primary Treatment		0.189		
Radical CCRT	29 (70.7%)			
Radical Surgery + Adjuvant (Chemo) Radiotherapy	12 (29.3%)			
Pattern of Failure		0.834		
Locoregional Recurrence Only	8 (19.5%)			
Distant Metastasis Only	27 (65.9%)			
Locoregional + Distant Metastasis	6 (14.6%)			
Pretreatment SCC-Ag (ng/mL)		0.030		
< 4.1 ng/ml	12 (29.3%)		Ref	
≥ 4.1 ng/ml	29 (70.7%)		0.185(0.051–0.665)	0.010
Number of Metastatic Lymph Nodes		0.217		
1	6 (14.6%)			
2	9 (22.0%)			
≥ 3	26 (63.4%)			
Pelvic Lymph Node Status		0.745		
Unilateral	17 (41,4%)			
Bilateral	24 (58.6%)			

Basic Characteristics	Univariable Cox analysis		Multivariate Cox analysis	
	n (%)	*p*	HR (95%)	*p*
Short-Axis Diameter of Largest Metastatic Node (cm)		0.335		
< 1	25 (61.0%)			
≥ 1	16 (39.0%)			
Maximum Tumor Diameter (cm)		0.163		
≤ 4	19 (46.3%)			
> 4	22 (53.7%)			
Progression-Free Survival (months)		0.007		
≤ 18.55	24 (58.5%)		Ref	
> 18.55	17 (41.5%)		5.339(1.812–16.088)	0.002

In the univariate analysis of PFS for the 41 patients with treatment failure, tumor maximum diameter showed a trend toward association with shorter PFS ($P = 0.083$). However, none of the examined variables, including tumor maximum diameter in multivariate analysis (P = 0.083), reached the conventional threshold of statistical significance ($P < 0.05$). Therefore, no independent prognostic factors for PFS were conclusively identified in this cohort. The detailed results are summarized in Table 2.

Table 2
Single-factor and multi-factor analysis of PFS influencing factors in cervical cancer patients who fail after treatment

Basic Characteristics	Univariable Cox analysis		Multivariate Cox analysis	
	n (%)	p	HR (95%)	p
Age (years)		0.892		
> 50	27 (65.9%)			
≤ 5	14 (34.1%)			
FIGO Stage (2018)		0.367		
C1	33 (80.4%)			
C2	8 (19.6%)			
Primary Treatment		0.439		
Radical CCRT	29 (70.7%)			
Radical Surgery + Adjuvant (Chemo) Radiotherapy	12 (29.3%)			
Pattern of Failure		0.887		
Locoregional Recurrence Only	8 (19.5%)			
Distant Metastasis Only	27 (65.9%)			
Locoregional + Distant Metastasis	6 (14.6%)			
Pretreatment SCC-Ag (ng/mL)		0.188		
< 4.1 ng/ml	12 (29.3%)		Ref	
≥ 4.1 ng/ml	29 (70.7%)		0.807(0.345–1.888)	0.621
Number of Metastatic Lymph Nodes		0.769		
1	6 (14.6%)			
2	9 (22.0%)			
≥ 3	26 (63.4%)			
Pelvic Lymph Node Status		0.512		
Unilateral	17 (41,4%)			
Bilateral	24 (58.6%)			

Basic Characteristics	Univariable Cox analysis		Multivariate Cox analysis	
	n (%)	p	HR (95%)	p
Short-Axis Diameter of Largest Metastatic Node (cm)		0.910		
< 1	25 (61.0%)			
≥ 1	16 (39.0%)			
Maximum Tumor Diameter (cm)		0.083		
≤ 4	19 (46.3%)		Ref	
> 4	22 (53.7%)		0.287(0.081–1.019)	0.053

3. Discussion

Stage IIIC CSCC represents a clinically aggressive disease with substantial heterogeneity in treatment response and survival outcomes[29]. Despite advances in multimodal therapy, including radical surgery, radiotherapy, and chemotherapy, the management of this subset remains challenging, with high rates of treatment failure and poor prognosis[29–31].

Our analysis reveals that distant metastasis was the dominant pattern of initial treatment failure, with lung metastasis being the most common site, and this finding aligns with growing evidence identifying it as a more pressing challenge than locoregional recurrence in advanced cervical cancer[32, 33]. Knoth J, et al. (2025) and Wark A, et al. (2025) reported distant metastasis rates of 14–27% in advanced-stage disease, consistent with our observed pattern. The lungs emerged as the most frequent site of distant involvement, a distribution corroborated by prior series[32]. The median time to recurrence in our cohort was 16 months, meaning that half of the patients experienced disease recurrence within this period. This finding is consistent with the established trend documented in the literature, where a significant proportion of recurrences are reported to occur within the first 2 to 3 years following primary therapy[34]. This underscores the systemic nature of treatment failure in stage IIIC disease, highlighting a critical need for effective systemic therapeutic strategies alongside optimized local control. While emerging data suggest that localized interventions (e.g., resection or SBRT for oligometastases) may benefit selected patients[35], their applicability is contingent upon effective systemic disease control, which remains the central unmet need.

We identified two independent predictors of poor overall survival following recurrence: a pre-treatment SCC-Ag level ≥ 4.1 ng/mL and a post-recurrence PFS of ≤ 18.55 months. The prognostic significance of elevated SCC-Ag is well-established and biologically plausible, as it reflects higher tumor burden, metastatic potential, and aggressive biology[36, 37]. Recent advances have refined the prognostic value of

SCC-Ag by integrating it with clinicopathological staging. For example, Huang XD et al. demonstrated that combining pretreatment SCC-Ag (cut-off 2.5 ng/mL) with FIGO stage formed a robust recursive partitioning analysis (RPA) model, which stratified early-stage cervical cancer into three distinct prognostic groups with significantly different overall survival. This model outperformed the FIGO 2018 staging system alone, highlighting SCC-Ag's critical role in risk stratification beyond conventional parameters. Building upon this refined risk stratification framework, our results directly corroborate the linking high SCC-Ag to increased recurrence risk and worse survival[38, 39]. However, our study advances this knowledge by specifically validating its power within the homogeneous, advances this knowledge high-risk stage IIIC CSCC cohort treated with radiotherapy, a context where its discriminatory value may be most clinically actionable. In our cohort, among the 41 patients who developed distant metastases, the lung was the most common site of failure (46.3%, 19/41). Separately, we observed that patients experiencing distant recurrence (including those with lung metastases) tended to have higher pretreatment SCC-Ag levels. These two complementary observations—the predominance of lung metastases and the association between high SCC-Ag and distant recurrence—converge to highlight a critical clinical need. They provide a rationale for investigating tailored post-radiotherapy surveillance strategies in future prospective studies. For instance, it would be reasonable to evaluate whether patients with high SCC-Ag levels benefit from more frequent or intensive thoracic imaging, potentially enabling a more personalized, risk-adapted management approach.

Moreover, our analysis identified a post-recurrence PFS of ≤ 18.55 months as an independent prognostic factor for poor overall survival. This 18.55-month threshold effectively dichotomizes the cohort, with patients experiencing early progression (PFS ≤ 18.55 months) showing worse outcomes compared to those with longer PFS.A short PFS (≤ 18.55 months) likely signifies inherent therapeutic resistance, aggressive tumor biology, or the presence of widespread disease at recurrence. In contrast to the baseline factors that dominate existing prognostic models[40],our analysis suggests that this early progression interval (PFS ≤ 18.55 months) may be a potential predictor of post-recurrence survival, which could offer a novel perspective for risk stratification in this patient population. This approach acknowledges that the disease trajectory after first-line failure carries critical prognostic information. The combination of a baseline biomarker (SCC-Ag) and a post-treatment clinical endpoint (PFS) may provides a more comprehensive, sequential risk assessment model than either factor alone.

Integrating these findings, we propose a three-step sequential management framework for stage IIIC CSCC. First, pre-treatment stratification using SCC-Ag (≥ 4.1 ng/mL) identifies high-risk patients, warranting intensified staging or treatment within clinical trials. Second, the observed pattern of early distant metastasis justifies an intensified surveillance protocol with systemic and imaging-based follow-up, especially within the initial 16-month period post-treatment for high-risk patients. Finally, upon recurrence, a PFS ≤ 18.55 months defines a subgroup with a dire prognosis, which should trigger immediate, aggressive, and multidisciplinary evaluation for salvage therapies, with prioritization for clinical trials of novel agents.

Our study has several important limitations. First, its retrospective, single-center design may introduce selection bias and limit the generalizability of our findings to broader populations. Second, the relatively limited sample size, particularly within subgroup analyses (e.g., the SCC-Ag-High group), constrains statistical power and may preclude the detection of more subtle associations. Finally, as with any non-randomized study, unmeasured confounding factors could have influenced the observed outcomes despite our multivariate adjustments.

Despite these constraints, our findings delineate clear and actionable priorities for future investigation. First, prospective, multi-center studies with larger cohorts are imperative to validate the prognostic model and precisely identify the truly high-risk population. Second, research should transition from prognostication to intervention. Prospective trials are warranted to evaluate whether intensified upfront treatment (e.g., adjuvant systemic therapy) for SCC-Ag-high patients improves outcomes. Finally, and critically, dedicated studies must define the optimal salvage regimen for patients with early progression (PFS ≤ 18.55 months), a population currently with severely limited options.

4. Conclusion

This study identifies distant metastasis as the predominant pattern of treatment failure in stage IIIC CSCC following definitive radiotherapy. Moreover, SCC-Ag ≥ 4.1 ng/mL and PFS ≤ 18.55 months are confirmed as independent predictors of relatively inferior overall survival. Enhanced systemic therapy should be prioritized for patients with these two risk factors to improve treatment efficacy.

Abbreviations

Abbreviation	Full Name
CC	Cervical Cancer
CCRT	Concurrent Chemoradiotherapy
CSCC	Cervical Squamous Cell Carcinoma
CTV	Clinical Target Volume
EFRT	Extended Field Radiation Therapy
FIGO	International Federation of Gynecology and Obstetrics
GTV	Gross Tumor Volume
HU	Hounsfield Units
IMRT	Intensity-Modulated Radiation Therapy
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
OS	Overall Survival
PFS	Progression-Free Survival
RECIST	Response Evaluation Criteria in Solid Tumors
SCC-Ag	Squamous Cell Carcinoma Antigen
SLN	Sentinel Lymph Node

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University (Approval No. 2025-E1033), and the requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

LLQ, QFH and SJZ designed the research protocol, collected clinical data, conducted the study, and drafted the manuscript. SSM, WMH and WYL contributed to the data analysis and interpretation. LJ and TTH provided the analysis tools and were also involved in revising the manuscript critically for important intellectual content. FW and YZ conceived the research idea, provided guidance throughout the study, and revised the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript.

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Data Availability

The datasets analysed during the current study are not publicly available due to the protection of patient privacy and confidentiality, but are available from the corresponding author on reasonable request, subject to institutional ethical approval and data use agreements.

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Figures

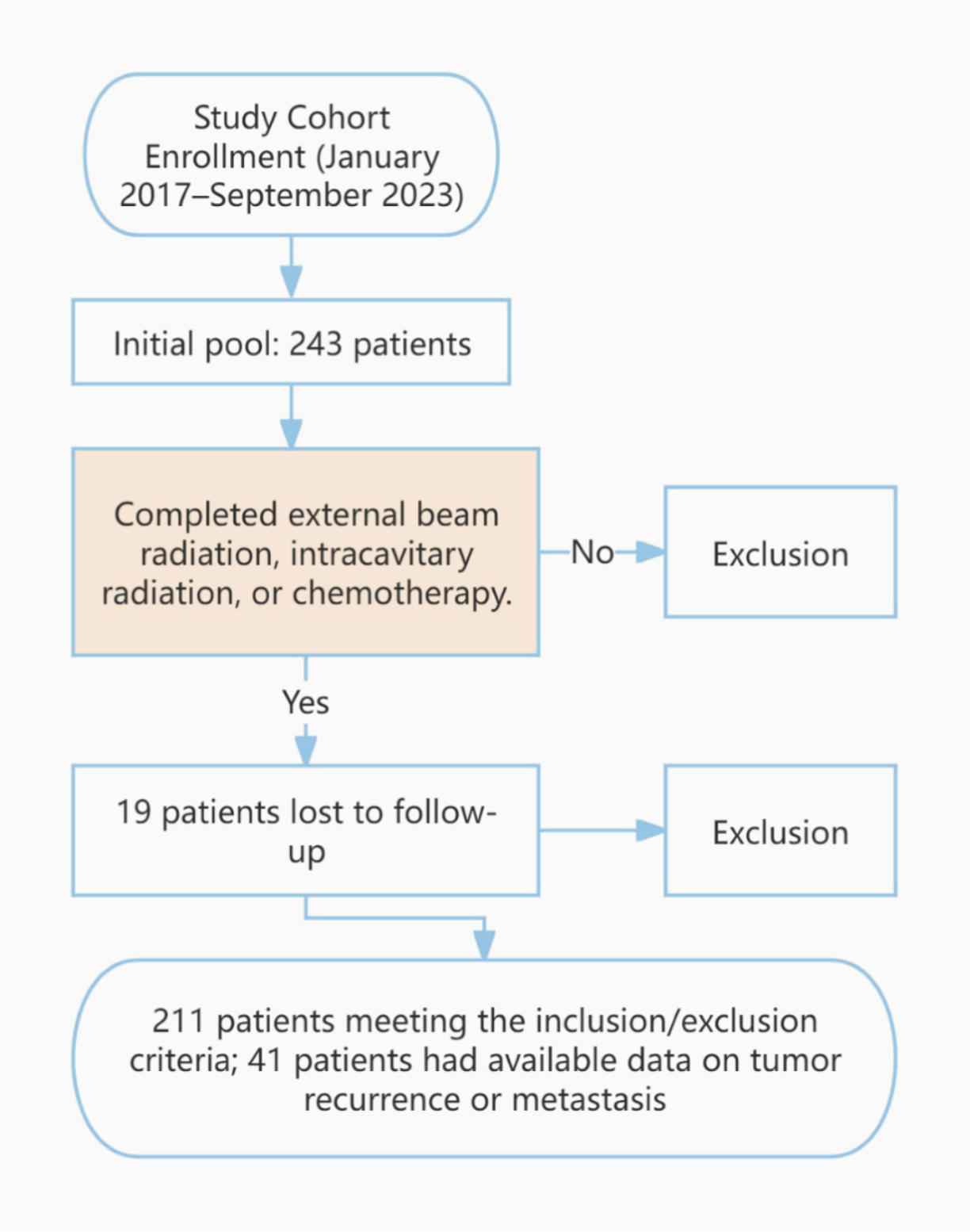


Figure 1

Flowchart of patient selection. Of 243 patients with stage IIIC CSCC, 32 were excluded (13 incomplete treatment, 19 lost to follow-up), yielding 211 eligible patients; recurrence or metastasis data were available for 41.

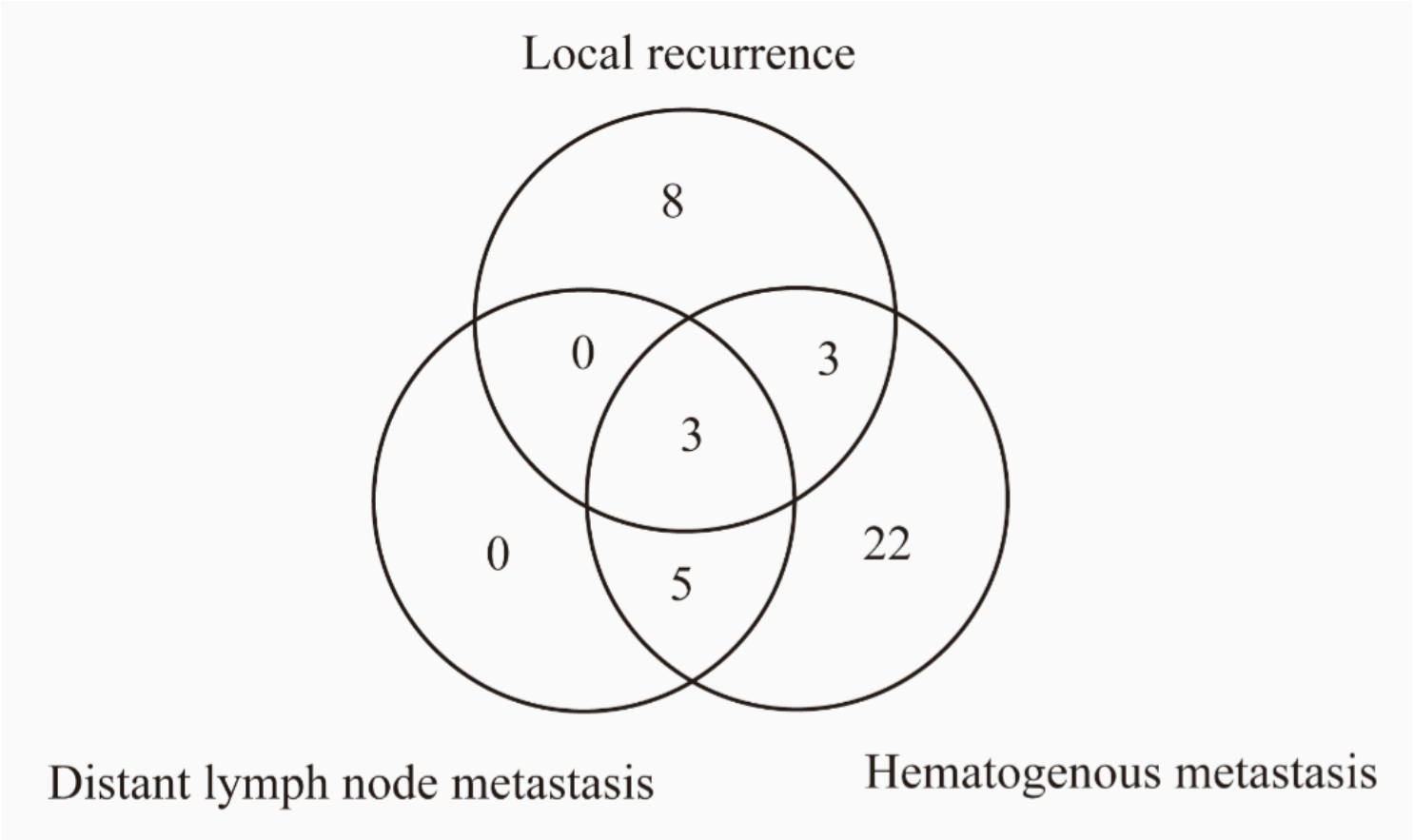


Figure 2

Distribution of treatment failure sites in patients with stage IIIC CSCC. The chart illustrates the number of patients experiencing pelvic (local) recurrence, distant lymph node metastasis, or hematogenous metastasis. Distant lymph node metastasis (n=8) was the most common site of treatment failure, followed by hematogenous metastasis (n=33) and pelvic recurrence (n=14).

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