Int J Clin Exp Med 2025;18(8):220-231
www.ijcem.com /ISSN:1940-5901/IJCEM0164383

Original Article

A retrospective analysis of 143 patients: unraveling clinical-pathological factors associated with recurrence patterns and time to recurrence in recurrent cervical cancer

Yanli Mo[1,4*], Qiang Huang[2*], Yujun He[3], Jiayin Peng[5*], Jiebo Yin[1*]

[1]Department of Oncology, Central People's Hospital of Zhanjiang, Zhanjiang 524000, Guangdong, China; [2]Department of Ultrasound, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, Guangdong, China; [3]Guangdong Medical University, Zhanjiang 524000, Guangdong, China; [4]Department of Pulmonary Oncology, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, Guangdong, China; [5]Department of Urology, Central People's Hospital of Zhanjiang, Zhanjiang 524000, Guangdong, China. [*]Equal contributors.

Received March 7, 2025; Accepted June 23, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Objective: This study aimed to investigate the clinical characteristics and prognostic factors of recurrent cervical cancer to optimize risk stratification and therapeutic strategies. Methods: A retrospective cohort study was conducted on 143 recurrent cases identified from 1,127 cervical cancer patients treated at two tertiary hospitals between August 2009 and May 2023. Chi-square tests, Kaplan-Meier survival analysis, and Cox proportional hazards models were employed to evaluate recurrence patterns, time-to-recurrence (TTR), and prognostic determinants. Results: The recurrence rate was 12.67% (143/1,127), with a median TTR of 15 months (IQR: 10-36). Distant metastases predominantly involved the lungs (31.6%), lymph nodes (24.1%), and bones (20.3%), with bone metastases occurring earliest (median: 12.5 months). Lymphovascular space invasion (LVSI), tumor size > 4 cm, advanced FIGO stage, and treatment modality significantly influenced TTR (all $P < 0.05$). Non-radiated patients exhibited localized recurrence (60.7%), whereas irradiated patients showed systemic dissemination (extrapelvic recurrence: 47.7%). In the postoperative recurrence subgroup (n = 121), univariate analysis identified tumor size > 4 cm ($P = 0.013$), advanced FIGO stage ($P < 0.001$), and adjuvant radiotherapy ($P = 0.013$) as independent predictors of early recurrence (TTR ≤ 12 months). Notably, irradiated patients demonstrated shorter median TTR (13 vs. 23 months, $P = 0.013$), attributable to higher baseline tumor burden (tumor > 4 cm: 29.2% vs. 12.5%, $P = 0.044$). Multivariate Cox regression revealed borderline significance for tumor size > 4 cm (HR = 1.450, 95% CI: 0.914-2.300, $P = 0.115$), advanced FIGO stage (HR = 1.228, 95% CI: 0.991-1.521, $P = 0.060$), and adjuvant radiotherapy (HR = 1.413, 95% CI: 0.966-2.068, $P = 0.075$). Conclusion: Tumor burden (size, stage, nodal involvement) drives recurrence patterns and timing. The paradoxical association between adjuvant radiotherapy and early recurrence highlights selection bias in high-risk cohorts. Our findings underscore the necessity of molecularly informed risk stratification to optimize therapeutic decision-making.

Keywords: Cervical cancer, recurrent, clinical-pathological, recurrence pattern, time to recurrence

Introduction

Cervical cancer remains a leading gynecological malignancy, imposing substantial burdens on women's health globally. While therapeutic advancements in surgery and radiotherapy have improved early-stage disease management, post-treatment recurrence persists as a critical clinical dilemma. The 2018 FIGO staging system reveals a steep escalation in stage-dependent recurrence rates from 10% in stage IB to 74% in stage IVA, with over 80% of these events clustering within the first two years post-treatment [1], highlighting the aggressive nature of residual disease and the critical window for surveillance. The management of recurrent cervical cancer faces unique challenges, particularly in radiotherapy-naïve populations. Nearly 70% of recurrent cases involve patients with prior pelvic irradiation [2], which complicates

https://doi.org/10.62347/UKCB4796

retreatment due to cumulative radiation toxicity and compromised tissue tolerance. Moreover, recurrent disease portends a dismal prognosis, with 1-year survival rates plunging below 15% [3], necessitating urgent investigations into recurrence drivers and risk stratification.

Emerging evidence has delineated clinicopathological determinants of cervical cancer recurrence, with large-scale meta-analyses confirming that FIGO stage, lymph node metastasis, tumor diameter, and therapeutic modalities (surgery, radiotherapy, chemotherapy, or combinations) independently correlate with post-treatment recurrence risks [4, 5]. Crucially, surgical radicality, radiation dosimetry, and chemotherapy sensitivity collectively orchestrate recurrence dynamics through tumor microenvironment remodeling [6, 7].

However, the specific mechanisms of action among these factors, as well as how to better predict and prevent recurrence, remain unclear. Therefore, further research on the factors influencing recurrence, particularly a comprehensive analysis of multiple factors and their potential interactions, is critical for improving treatment outcomes and prognosis. This study aims to provide a scientific basis for the development of personalized prevention and treatment strategies, with the goal of achieving breakthroughs in cervical cancer therapy.

Methods

Study population

This retrospective cohort study analyzed 143 patients with recurrent cervical cancer identified from 1,127 consecutively treated cases at the Affiliated Hospital of Guangdong Medical University and Zhanjiang Central People's Hospital between August 2009 and May 2023. Inclusion Criteria: ① Confirmed recurrence: Defined as either: Histopathological confirmation of recurrence (primary or metastatic lesions by biopsy); Radiological-clinical evidence (enhanced MRI/CT/PET-CT demonstrating pelvic masses, lymphadenopathy, or distant metastases) that met the RECIST 1.1 criteria. ② Prior antitumor treatment: At least one therapeutic intervention (surgery, radiotherapy, chemoradiotherapy, or combinations). Exclusion Criteria: ① Concurrent malignancies; ② Ambiguous pathology or non-cervical primary carcinoma; ③ Significant comorbidities (e.g., uncontrolled cardiopulmonary diseases); ④ De novo stage IV disease or pretreatment distant metastases. Participants were stratified into three age cohorts: young-middle-aged (30-44 years), middle-elderly (45-59 years), and elderly (≥ 60 years). Ethical approval was obtained from the Institutional Review Board of Zhanjiang City, China (Approval No.: PJ[IIT-2024026-2]; November 11, 2024), with a waiver of informed consent granted due to the retrospective design.

Data collection

Clinicopathological data were systematically retrieved, including age at diagnosis, histological type (squamous/adenocarcinoma/other subtypes), maximum tumor diameter (≤ 4 cm or > 4 cm), lymphovascular space invasion (LVSI) status, 2018 FIGO staging, metastatic lymph node count/location, surgical procedures, and therapeutic regimens. Pathological evaluations adhered to international consensus guidelines: primary tumor dimensions (millimeter precision) and stromal invasion depth were recorded, along with growth patterns (exophytic/endophytic). Systematic pelvic lymphadenectomy encompassed the external iliac, obturator, internal iliac, and common iliac nodal groups. Parametrial involvement was defined as a tumor ≤ 3 mm from resection margins.

Recurrence patterns were classified by prior radiotherapy exposure: Post-radiotherapy recurrence group: a) In-field recurrence: Recurrence within the original radiotherapy fields, including the cervix, upper vagina, or parametria; b) Out-field recurrence: Distant metastases outside the original radiotherapy fields (e.g., lung, bone, or intra-abdominal sites); c) Both in-field and out-of-field: Concurrent in-field and out-field recurrences.

Radiotherapy-naïve group: a) Central recurrence: Relapse in the uterus, parametria, or vaginal vault; b) Peripheral recurrence: Extrapelvic metastases; c) Composite type: Combined central and peripheral recurrences [8].

2018 FIGO Staging Criteria: Stage I: Confined to the cervix (uterine extension permitted). Stage II: Beyond the cervix but not involving pelvic wall/lower vagina: IIA: Upper 2/3 vaginal invasion without parametrial involvement; IIB: Parametrial invasion. Stage III: Extends to pelvic

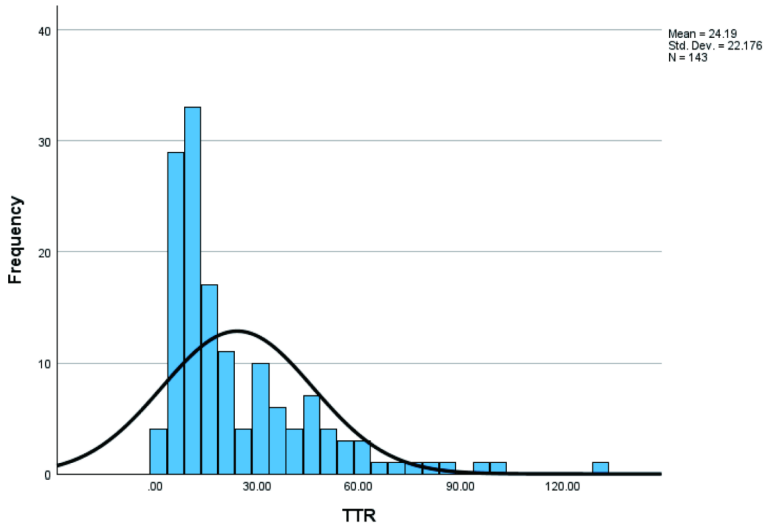

Figure 1. Cervical cancer recurrence time distribution and frequency histogram.

wall/lower vagina, causes hydronephrosis, or nodal metastasis. IIIA: Lower 1/3 vaginal involvement; IIIB: Pelvic wall invasion/hydronephrosis; IIIC: Nodal metastasis (IIIC1: pelvic; IIIC2: para-aortic) with imaging (r) or pathological (p) designation. Time-to-Recurrence (TTR) was defined as the interval from initial treatment commencement to histopathological/radiological confirmation (RECIST 1.1) of first recurrence. Right-censoring was applied for loss-to-follow-up or recurrence-free cases at last contact. Postoperative recurrences were dichotomized as early (TTR ≤ 12 months) or late (TTR > 12 months).

Follow-up protocol

The follow-up period commenced at the completion date of primary tumor therapy. The endpoint was defined as the date of first recurrence confirmation or the last follow-up (May 2023). Primary outcome: TTR. Secondary outcomes: Recurrence patterns and survival status (alive/deceased). Follow-up evaluations were conducted at 3-month intervals (gynecological examination + cross-sectional imaging) and 6-month intervals (serum tumor marker assays). The median follow-up duration was 30 months.

Statistical analysis

A structured database was constructed using Microsoft Excel 2019, with data integrity ensured through dual-independent entry and cross-verification. Analyses were performed in SPSS Statistics 29.0. Categorical variables (e.g., tumor size, histology) were summarized as frequencies (percentages), while non-normally distributed continuous variables were reported as medians with interquartile ranges (IQR). Univariate analyses: Associations between categorical variables were assessed via Pearson's chi-square test; relationships between continuous and categorical variables were evaluated using nonparametric tests (Mann-Whitney U/Kruskal-Wallis H). Survival analysis: TTR was estimated via the Kaplan-Meier method; intergroup TTR differences were compared by log-rank test; Cox proportional hazards models generated hazard ratios (HR) with 95% confidence intervals (CI). All tests were two-tailed, with statistical significance set at $P < 0.05$.

Results

Clinical characteristics of recurrent cervical cancer

A total of 143 patients with recurrent cervical cancer were included (overall cohort: 1,127; recurrence rate: 12.67%). The median TTR was 15 months (IQR: 10-36), with a right-skewed distribution (**Figure 1**). Distant metastases occurred in 79 patients (55.2%), exhibiting organotropism: the most common site was the lungs (31.6%, 25/79), followed by lymph nodes (24.1%, 19/79), bone (20.3%, 16/79), and liver (17.7%, 14/79), while brain (5.1%, 4/79) and thyroid (1.3%, 1/79) metastases were rare. Temporal analysis revealed bone as the earliest metastatic site (median: 12.5 months), followed sequentially by lymph nodes (13 months), lungs (13 months), liver (18 months), brain (21 months), and thyroid (22 months).

Prognostic factors for TTR

Nonparametric analyses demonstrated significant heterogeneity in TTR across risk-stratified subgroups (**Table 1**). Pathological Features: LVSI: Kruskal-Wallis test confirmed LVSI status

Table 1. Clinicopathologic characteristics and Time to Recurrence (TTR) of recurrent cervical cancer

Characteristic	N	%	Time to recurrence TTR (m)	
			Statistical Test	*P-value*
Age (years)			1.949	0.377
30-44	22	15.4		
45-59	67	46.9		
≥ 60	54	37.8		
Pathological type			0.886	0.642
Squamous cell carcinoma	110	76.9		
Adenocarcinoma	21	14.7		
Other rare types	12	8.4		
LVSI			9.239	0.010
No	39	27.3		
Yes	70	49.0		
Uncertain	34	23.8		
Tumor size			1342.000	< 0.001
≤ 4 cm	100	69.9		
> 4 cm	43	30.1		
FIGO stage			10.256	0.006
Early-stage Group (IA-IIA)	82	57.3		
Locally Advanced Group (IIB-IIIB)	29	20.3		
Lymph Node Metastasis Group (IIIC1-IIIC2)	32	22.4		
Number of lymph node metastasis			2.466	0.291
0	82	57.3		
1-3	42	29.4		
≥ 4	19	13.3		
Region of lymph node metastasis			4.547	0.103
None	77	53.8		
Pelvic	58	40.6		
Peri-aortic or para-aortic abdominal	7	4.9		
Inguinal	1	0.7		
Surgery			918.000	0.021
Yes	121	84.6		
No	22	15.4		
Postoperative radiotherapy			1382.500	0.023
No	56	46.3		
Yes	65	53.7		
Treatment strategy			9.266	0.010
Surg.	47	32.9		
Surg.+RT/RCT/Chemo	75	52.4		
RCT/RT	21	14.7		
Pattern of recurrence			9.996	0.075
Central	36	25.2		
Peripheral	11	7.7		
Composite	13	9.1		
Out-of-field	44	30.8		
In-field	28	19.6		
Both in-field and out-of-field	11	7.7		

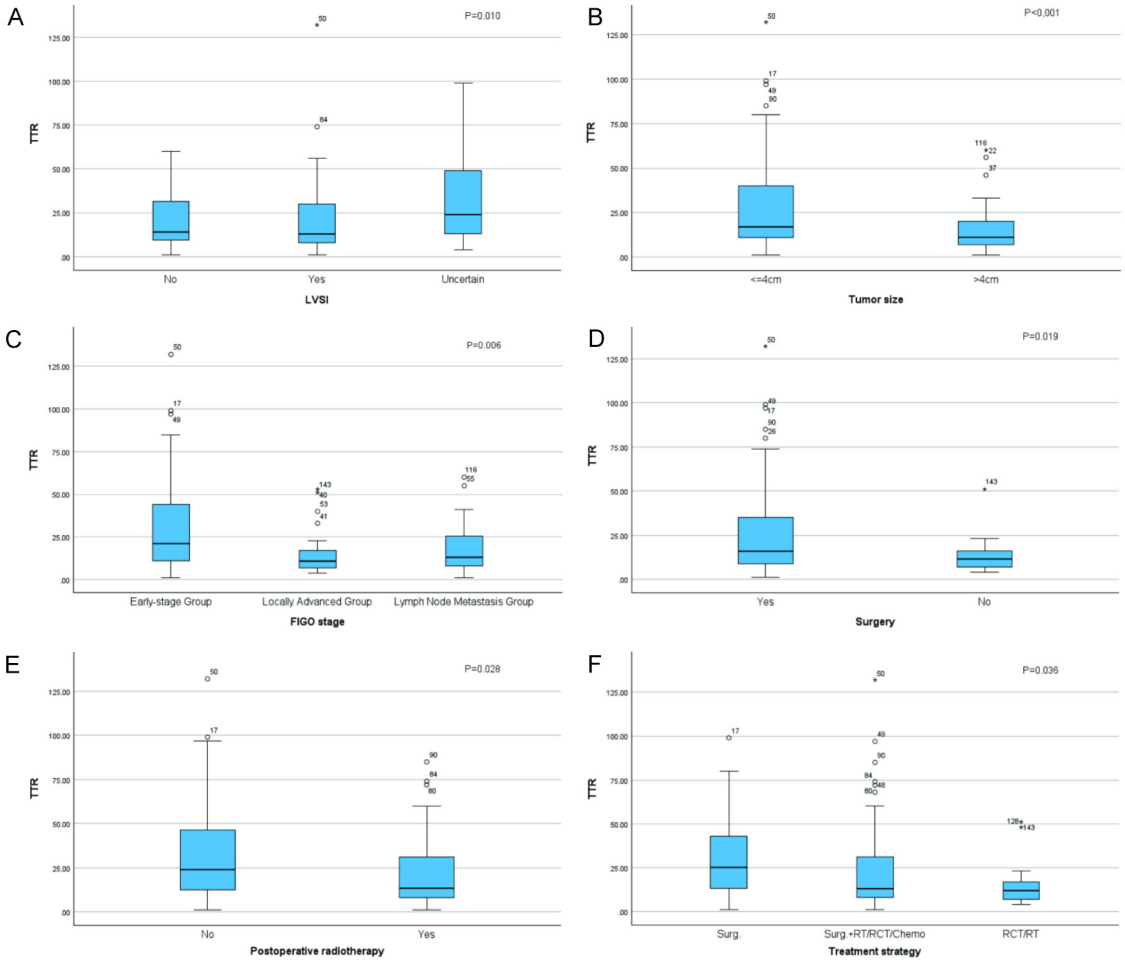

Figure 2. Distribution of Time to Recurrence (TTR) by different groups with statistically significant *P*-values. Each box plot displays the median, interquartile range (IQR), and outliers. P-values (displayed above each plot) indicate significant differences between groups, as determined by non-parametric tests (Kruskal-Wallis H test and Mann-Whitney U test). Outliers are shown as individual points beyond 1.5×IQR. LVSI, lymphovascular space invasion; Surg, surgery; Chemo, chemotherapy; RT, radiotherapy; RCT, radiochemotherapy.

significantly influenced TTR (H = 9.239, P = 0.010). The LVSI-uncertain group had a prolonged median TTR (24.0 months) compared to the LVSI-defined group (positive/negative: 14.0 months; Dunn's post hoc test with Bonferroni correction, $P < 0.05$). No significant difference existed between LVSI-positive and negative subgroups (adjusted P = 1.735). Tumor size: The > 4 cm group showed a markedly shorter median TTR (11.0 months vs. 19.5 months; Mann-Whitney U = 1342, $P < 0.001$). Disease Staging: Early-stage group (IA-IIA2): Median TTR = 21.0 months. Locally advanced (IIB-IIIB) and nodal metastasis (IIIC1-IIIC2) groups: Median TTR decreased to 10.0 and 13.0 months, respectively (Kruskal-Wallis H = 10.256, P = 0.006). Box plots (**Figure 2A-F**) illustrated significant TTR variations driven by LVSI status, tumor size, FIGO stage, surgical approach, radiotherapy, and treatment strategy (all $P < 0.05$).

Anatomical drivers of recurrence patterns

Chi-square analysis (**Table 2**) revealed significant associations between recurrence patterns and tumor size, FIGO stage, metastatic lymph node count, and nodal distribution (all $P < 0.05$). Tumors ≤ 4 cm predominantly exhibited central recurrence (91.7%, 33/36), significantly exceeding the proportion in tumors > 4 cm (8.3%, $P < 0.001$). Conversely, tumors > 4 cm demonstrated higher rates of out-of-field recurrence (53.5%) and both in-field and out-of-field recurrence (11.6%). Locally advanced group (IIB-IIIB): Out-of-field recurrence rate was 48.3%

Table 2. Recurrent cervical cancer recurrence patterns based on various clinicopathological characteristics

Characteristic	Pattern of recurrence						χ^2	P
	Central	Peripheral	Composite	Out-of-field	In-field	Both in-field and out-of-field		
Age (years)							5.258	0.873
30-44	6	4	2	6	3	1		
45-59	17	3	6	22	14	5		
≥ 60	13	4	5	16	11	5		
Pathological type							9.889	0.450
squamous cell carcinoma	27	6	11	37	21	8		
Adenocarcinoma	6	2	1	4	5	3		
Other rare types	3	3	1	3	2	0		
LVSI							13.101	0.218
No	14	5	4	9	6	1		
Yes	14	5	4	9	6	1		
Uncertain	11	2	3	10	4	4		
Tumor size							22.277	< 0.001
≤ 4 cm	33	10	10	21	20	6		
> 4 cm	3	1	3	23	8	5		
FIGO stage								
Early-stage Group (IA-IIA)	30	8	7	17	15	5	29.215	0.001
Locally Advanced Group (IIB-IIIB)	0	2	2	14	10	1		
Lymph Node Metastasis Group (IIIC1-IIIC2)	6	1	4	13	3	5		
Number of lymph node metastasis							29.352	0.001
0	30	9	8	19	12	4		
1-3	4	2	4	15	14	3		
≥ 4	2	0	1	10	2	4		
Region of lymph node metastasis							31.078	0.009
None	29	9	8	16	12	3		
Pelvic	6	2	4	24	15	7		
Peri-aortic or para-aortic abdominal	1	0	1	4	0	1		
Inguinal	0	0	0	0	1	0		

(14/29), exceeding that of the early-stage group (IA-IIA2) (20.7%, 17/82). Nodal metastasis group (IIIC1-IIIC2): Both in-field and out-of-field recurrence occurred in 15.6% (5/32), reflecting multifocal dissemination. Demographic characteristics (age stratification) and histopathological parameters (histological subtype) showed no significant association with recurrence patterns (all $P > 0.05$).

Characteristics of postoperative recurrence subgroup

In the postoperative recurrence cohort (n = 121), the median TTR was 16 months (IQR: 12-36). Significant heterogeneity in recurrence pattern distribution was observed across tumor size ($\chi^2 = 12.694$, $P = 0.026$), FIGO stage ($\chi^2 = 20.250$, $P = 0.027$), metastatic lymph node count ($\chi^2 = 20.927$, $P = 0.022$), nodal distribution ($\chi^2 = 20.554$, $P = 0.024$), and postoperative radiotherapy ($\chi^2 = 106.821$, $P < 0.001$). Non-irradiated group (n = 56): Predominant central recurrence (60.7%, 34/56). Irradiated group (n = 65): Extrapelvic recurrence (47.7%, 31/65) and systemic dissemination patterns. No significant intergroup differences were noted for age stratification ($\chi^2 = 6.103$, $P = 0.807$), histological type ($\chi^2 = 11.223$, $P = 0.340$), or lymphovascular space invasion (LVSI) status ($\chi^2 = 15.794$, $P = 0.106$).

Univariate Analysis: Chi-square tests (**Table 3**) identified tumor size > 4 cm ($P = 0.008$), LVSI ($P = 0.002$), and postoperative radiotherapy ($P = 0.025$) as independent predictors of early recurrence (TTR ≤ 12 months). Kaplan-Meier curves (**Figure 3**) demonstrated: Tumor size > 4 cm: Median TTR = 11 months (95% CI: 7.263-14.737), 7 months shorter than the ≤ 4 cm group (18 months, 95% CI: 10.837-25.163; Log-Rank $\chi^2 = 6.284$, $P = 0.012$). Early-stage group

Table 3. Clinicopathological predictors of postoperative early (≤ 12 months) and late (> 12 months) recurrence in cervical Cancer

Characteristic	Total (n = 121)	Early Recurrence (n = 43)	Late Recurrence (n = 78)	χ^2	P
Age (years)				4.118	0.128
30-44	20	4	16		
45-59	57	19	38		
≥ 60	44	20	24		
Pathological type				1.199	0.549
squamous cell carcinoma	91	33	58		
Adenocarcinoma	19	5	14		
Other rare types	11	5	6		
LVSI				12.605	0.002
No	39	15	24		
Yes	59	27	32		
Uncertain	23	1	22		
Tumor size				7.096	0.008
≤ 4 cm	95	28	67		
> 4 cm	26	15	11		
FIGO stage					
Early-stage Group (IA-IIA)	82	24	58	4.629	0.099
Locally Advanced Group (IIB-IIIB)	7	4	3		
Lymph Node Metastasis Group (IIIC1-IIIC2)	32	15	17		
Number of lymph node metastasis				0.001	1.000
0	79	28	51		
1-3	28	10	18		
≥ 4	14	5	9		
Region of lymph node metastasis				1.757	0.415
None	74	23	51		
Pelvic	43	18	25		
Peri-aortic or para-aortic abdominal	4	2	2		
Postoperative radiotherapy				5.053	0.025
No	56	14.0	42		
Yes	65	29.0	36		

(IA-IIA): Median TTR = 21 months (95% CI: 15.541-26.459). Locally advanced (IIB-IIIB) and nodal metastasis (IIIC1-IIIC2) groups: Median TTR decreased to 10 months (95% CI: 7.434-12.566) and 13 months (95% CI: 10.800-15.200), respectively (Log-Rank χ^2 = 7.012, *P* = 0.030). Postoperative radiotherapy: Median TTR was significantly shorter than non-irradiated cases (13 vs. 23 months, *P* = 0.013). Baseline disparities: The irradiated group exhibited higher tumor burden: Tumor > 4 cm: 29.2% vs. 12.5% (*P* = 0.044); LVSI positivity: 60.0% vs. 35.7% (*P* = 0.024); Nodal metastasis burden: 1-3 nodes: 27.7% vs. 17.9%; ≥ 4 nodes: 16.9% vs. 5.4% (*P* = 0.033).

Multivariate Analysis: The Cox proportional hazards model demonstrated overall significance (χ^2 = 14.295, *P* = 0.003). Tumor size > 4 cm (HR = 1.450, 95% CI: 0.914-2.300, *P* = 0.115), advanced FIGO stage (HR = 1.228, 95% CI: 0.991-1.521, *P* = 0.060), and postoperative radiotherapy (HR = 1.413, 95% CI: 0.966-2.068, *P* = 0.075) were associated with elevated recurrence risk, though statistical significance was not achieved, suggesting potential residual confounding or limited sample size.

Discussion

The overall recurrence rate in our cohort (12.67%) was significantly lower than in pre-

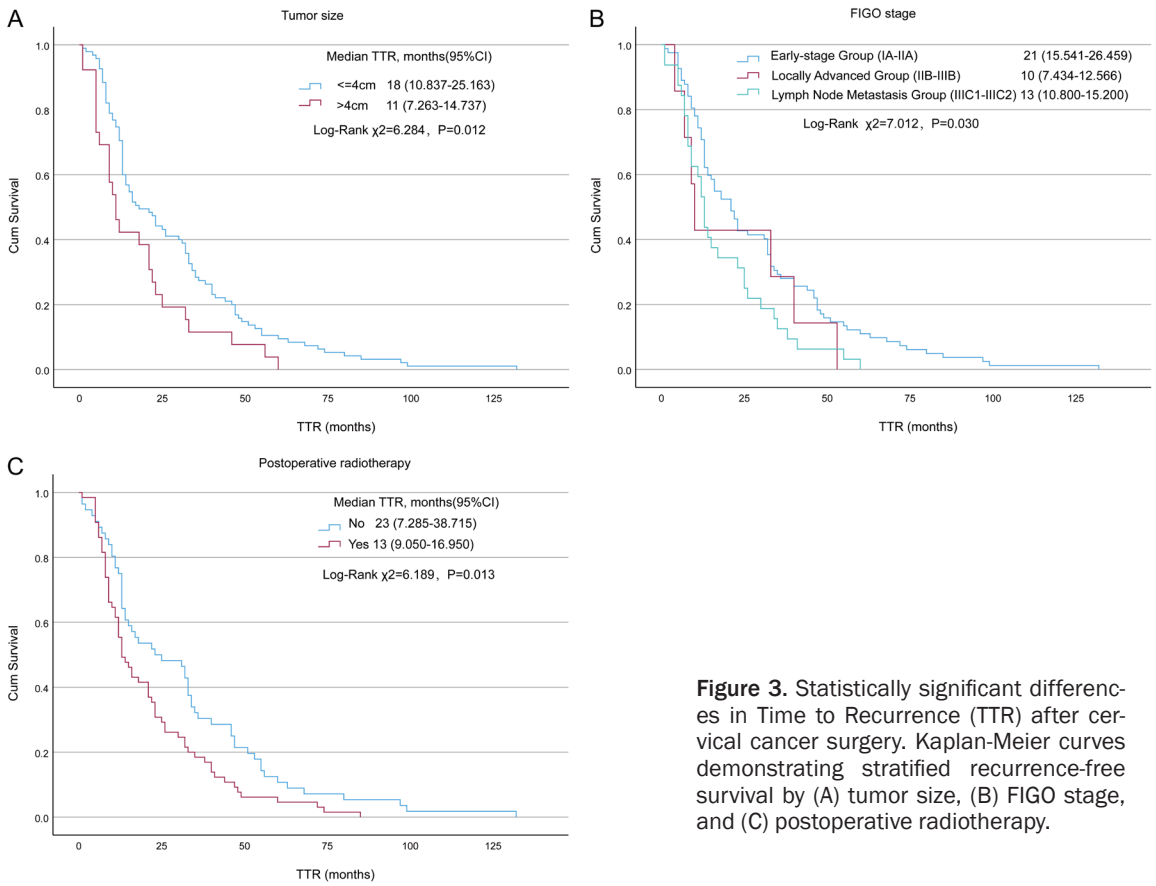

Figure 3. Statistically significant differences in Time to Recurrence (TTR) after cervical cancer surgery. Kaplan-Meier curves demonstrating stratified recurrence-free survival by (A) tumor size, (B) FIGO stage, and (C) postoperative radiotherapy.

viously reported population-based studies (22.3%-26%) [9-11]. This discrepancy likely reflects advancements in multidisciplinary therapeutic strategies, particularly the widespread adoption of concurrent chemoradiotherapy (CCRT) and integration of targeted therapies. Supporting this, Renxian Xie et al. demonstrated a 5-year recurrence rate of only 9.7% in CCRT-treated patients versus 20.4% in surgery-alone cohorts [12]. Furthermore, Hua Yang's team reported that combining bevacizumab with CCRT improved complete response rates to 66.1% and 4-year survival to 78.6%, underscoring the synergistic efficacy of anti-angiogenic agents and locoregional radiotherapy in suppressing recurrence [13].

Our study identified pulmonary metastases as the most common distant recurrence site (31.6%), aligning with Jie Shen's analysis of 572 metastatic cases where lung and bone ranked as the top two sites [14]. Notably, bone metastases occurred earliest in our cohort (median: 12.5 months), suggesting hematogenous dissemination dominates early recurrence, a finding complementary to Shen's conclusion that "bone metastases warrant prioritized radiotherapy intervention" [14]. This temporal pattern provides novel rationale for refining surveillance protocols. Based on our data, we propose 12-18 months post-treatment as a critical window for bone metastasis screening, advocating low-dose CT combined with whole-body bone scintigraphy to enhance detection sensitivity.

In this cohort, 65.7% of recurrences occurred within two years (median TTR: 15 months, IQR: 10-36), aligning closely with the 75% two-year recurrence rate reported for locally advanced cervical cancer patients undergoing definitive chemoradiotherapy [9]. This consistency suggests that recurrence timing may exhibit predictable patterns influenced by therapeutic modalities. Our findings highlight the intricate interplay among lymphovascular space invasion (LVSI), tumor size, FIGO stage, nodal metastasis, and treatment strategies, which is critical for deciphering the biological behavior of recurrent cervical cancer and refining clinical decision-making.

Recurrent cases predominantly affected women aged 45-59 years (46.9%). While Kruskal-Wallis tests revealed no independent age-stratified impact on TTR (P = 0.377), Kaplan-Meier curves suggested clinically relevant trends: the ≥ 60 subgroup exhibited the shortest median TTR (13 months; 95% CI: 1.83-9.399), compared to the 30-44 subgroup (16 months; 95% CI: 6.807-25.193) and 45-59 subgroup (15 months; 95% CI: 10.990-19.010). Though intergroup differences lacked statistical significance (Log-Rank P = 0.544), this trend may reflect age-related immune decline and therapeutic toxicity tolerance concerns in elderly patients [15-17].

Squamous cell carcinoma (SCC) dominated histologically (73.4%), yet Kruskal-Wallis analysis showed no independent association between histological subtype and TTR (P = 0.642). Divergent from the findings of Vinh-Hung et al. [18], which leveraged SEER data (1973-2002) to categorize long-term prognosis by histopathological subtypes - ordered as SCC, adenocarcinoma, adenosquamous carcinoma, mucinous carcinoma, and small cell carcinoma - their analysis demonstrated significantly elevated mortality hazards for adenocarcinoma (HR = 1.52) and adenosquamous carcinoma (HR = 1.35) relative to SCC (both P < 0.001). Their analysis employed overall survival, spanning from initial diagnosis to death, whereas our study focused on TTR to assess primary tumor containment. This divergence implies that the prognostic disadvantage of non-SCC subtypes may manifest predominantly in post-recurrence phases.

Consistent with literature documenting younger age and higher recurrence/mortality risks in adenocarcinoma [19, 20], our cohort showed a higher proportion of adenocarcinoma in the 30-44 subgroup (28.6%, 6/21) compared to SCC (13.6%, 15/110), though Pearson's χ^2 test did not reach significance (χ^2 = 7.880, P = 0.096). This attenuated association may stem from limited sample size and cohort heterogeneity, yet directionally supports the consensus that adenocarcinoma disproportionately affects younger women.

LVSI, a key histologic hallmark of aggressive cervical cancer biology, demonstrated significant associations with recurrence rates and TTR. A Danish cohort study [21] of primary early-stage cervical cancer (FIGO IA1-IB1) reported that LVSI positivity markedly increased recurrence risk (HR = 1.92, P = 0.0188), underscoring its prognostic value for early relapse. However, in our recurrent cohort, the LVSI-defined subgroup (positive/negative) exhibited comparable median TTR (14.0 months vs. 14.0 months), whereas the LVSI-uncertain subgroup showed prolonged TTR (24.0 months; P = 0.010). Chi-square tests revealed that LVSI status significantly influenced postoperative radiotherapy decisions (P = 0.033): LVSI-positive patients were more likely to receive adjuvant radiotherapy (59.4% in irradiated vs. 35.7% in non-irradiated groups), aligning with NCCN guidelines recommending radiotherapy for high-risk features. The lower radiotherapy rate in the LVSI-uncertain subgroup (25.0% non-irradiated vs. 14.1% irradiated) may reflect primary chemoradiation for non-surgical candidates. Radiotherapy may counteract LVSI-driven recurrence via microenvironment modulation. Future studies should integrate radiogenomics and liquid biopsy-based dynamic monitoring to refine radiotherapy beneficiary identification.

Tumor size and FIGO stage emerged as central prognostic determinants of recurrence patterns and TTR [22, 23]. Peiretti et al. [23] observed a recurrence risk escalation from 1.2% for tumors ≤ 2 cm to 21% for tumors > 2 cm. In our cohort, tumors ≥ 4 cm exhibited higher extrapelvic recurrence rates (34.9%) and greater likelihood of multimodal therapy (e.g., 50% increased chemoradiation use for tumors ≥ 6 cm), advocating aggressive strategies for high tumor burden. Conversely, tumors < 2 cm predominantly manifested central recurrence (47.1% surgery-only), possibly due to early-stage diagnosis and omitted adjuvant therapy. Escande et al. [24] reported that preoperative brachytherapy in IB1-IIA1 patients with tumors ≥ 3 cm reduced 5-year disease-free survival (P = 0.003), implicating residual micro-metastatic potential.

Our study identified tumor size > 4 cm as an independent predictor of early postoperative recurrence (TTR ≤ 12 months; P = 0.013). Beyond temporal truncation (7-month TTR reduction), tumors > 4 cm displayed systemic dissemination, with extrapelvic recurrence (53.5%) and both in-field and out-of-field recurrence (11.6%), reflecting hematogenous spread and nodal skip metastasis, strongly correlated with

advanced FIGO stages (IIB-IIIB) and ≥ 3 metastatic lymph nodes.

Although tumor size showed no direct association with LVSI positivity ($P = 0.535$), its anatomic constraints likely dictated metastatic routes. Tumors ≤ 4 cm, confined by anatomic barriers, preferentially recurred locally via direct invasion or lymphatic bypass. These findings underscore tumor burden's pivotal role, warranting integration of molecular subtyping and radiomics into personalized recurrence prediction models.

FIGO stage independently stratified TTR and recurrence patterns. The early-stage group (IA1-IIA2) exhibited prolonged median TTR (21.0 months) compared to locally advanced (IIB-IIIB; 10.0 months) and nodal metastasis (IIIC1-IIIC2; 13.0 months) groups ($P = 0.006$). This aligns with Wang et al.'s cervical adenocarcinoma recurrence model, where FIGO stage dominated RFS prediction. Liu et al.'s nomogram further validated tumor size and nodal metastasis as independent systemic recurrence drivers ($P = 0.001$) [25], corroborating our nodal subgroup's abbreviated TTR.

This study confirmed significant anatomical heterogeneity in postoperative recurrence patterns of cervical cancer, closely associated with tumor burden parameters (size, FIGO stage, nodal metastasis) and therapeutic strategies. Among 121 postoperative recurrence cases, non-irradiated patients predominantly exhibited localized progression, whereas irradiated patients demonstrated systemic dissemination. While postoperative radiotherapy was associated with a significantly shorter median TTR (13 vs. 23 months, $P = 0.013$), its impact in the multivariate Cox model was borderline nonsignificant ($P = 0.075$). This paradox likely stems from treatment selection bias favoring high-risk patients (larger tumors, heavy nodal burden, LVSI positivity, advanced stage) for adjuvant radiotherapy. Despite comprehensive adjustment for established confounders in our multivariate model, residual confounding may persist due to unmeasured variables. These include molecular heterogeneity and technical variations in radiotherapy delivery (e.g., deviations from planned target volumes), both of which could theoretically distort hazard ratio estimations.

Limitations

This study has limitations: Retrospective design: Unavailable key prognostic variables (e.g., PD-L1 expression, HPV subtypes) might introduce bias; Sample size constraint (n = 143): Reduced power for multivariate Cox regression and rare event analyses (e.g., thyroid metastasis). Exclusion of non-recurrent cases precludes absolute recurrence risk calculation.

Conclusion

We systematically identified key drivers of cervical cancer recurrence. LVSI, tumor size, FIGO stage, nodal metastasis, and treatment modalities significantly predict recurrence patterns and TTR. These findings underscore the necessity for comprehensive recurrence management and urgent optimization of therapeutic strategies. Future multicenter studies with larger cohorts are imperative to validate and generalize these insights for clinical translation.

Acknowledgements

This study was supported by the Zhanjiang Science and Technology Bureau (2022A01084).

Disclosure of conflict of interest

None.

Address correspondence to: Jiayin Peng, Department of Urology, Central People's Hospital of Zhanjiang, No. 236, Yuanzhu Road, Chikan District, Zhanjiang 524023, Guangdong, China. E-mail: 373120-839@qq.com; Jiebo Yin, Department of Oncology, Central People's Hospital of Zhanjiang, No. 236, Yuanzhu Road, Chikan District, Zhanjiang 524023, Guangdong, China. E-mail: 281948517@qq.com

References

[1] Pfaendler KS and Tewari KS. Changing paradigms in the systemic treatment of advanced cervical cancer. Am J Obstet Gynecol 2016; 214: 22-30.

[2] Barney BM, Petersen IA, Dowdy SC, Bakkum-Gamez JN, Klein KA and Haddock MG. Intraoperative Electron Beam Radiotherapy (IOERT) in the management of locally advanced or recurrent cervical cancer. Radiat Oncol 2013; 8: 80.

[3] DiSaia PJ and Creasman WT. Clinical gynecologic oncology, 6th edition. St. Louis: Mosby; 2002.

[4] de Foucher T, Bendifallah S, Ouldamer L, Bricou A, Lavoue V, Varinot J, Canlorbe G, Carcopino X, Raimond E, Monnier L, Graesslin O, Touboul C, Collinet P, Neveu ME, Huchon C, Daraï E and Ballester M; Groupe de Recherche Francogyn, France. Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: retrospective multicentre study from the FRANCOGYN group. Eur J Surg Oncol 2019; 45: 659-665.

[5] Peng QH, Chen K, Li JY, Chen L and Ye WJ. Analysis of treatment outcomes and prognosis after concurrent chemoradiotherapy for locally advanced cervical cancer. Front Oncol 2022; 12: 926840.

[6] Chao X, Song X, Wu H, You Y, Wu M and Li L. Selection of treatment regimens for recurrent cervical cancer. Front Oncol 2021; 11: 618485.

[7] Kotaka S, Kondo E, Kawai Y, Okamoto K, Kishigami Y, Yamawaki T, Nagao K, Hirata T and Suzuki S. Real-world efficacy and safety of bevacizumab single-maintenance therapy following platinum-paclitaxel chemotherapy plus bevacizumab in patients with advanced cervical cancer. J Gynecol Oncol 2023; 34: e60.

[8] Kim TH, Kim MH, Kim BJ, Park SI, Ryu SY and Cho CK. Prognostic importance of the site of recurrence in patients with metastatic recurrent cervical cancer. Int J Radiat Oncol Biol Phys 2017; 98: 1124-1131.

[9] Yoshida K, Kajiyama H, Utsumi F, Niimi K, Sakata J, Suzuki S, Shibata K and Kikkawa F. A post-recurrence survival-predicting indicator for cervical cancer from the analysis of 165 patients who developed recurrence. Mol Clin Oncol 2018; 8: 281-285.

[10] Thongkhao P, Janmunee N and Tangkananan A. Prognostic factors for post-recurrence survival among patients with locally advanced cervical cancer who underwent definitive concurrent chemoradiation. Rep Pract Oncol Radiother 2022; 27: 615-623.

[11] Cibula D, Dostálek L, Jarkovsky J, Mom CH, Lopez A, Falconer H, Scambia G, Ayhan A, Kim SH, Isla Ortiz D, Klat J, Obermair A, Di Martino G, Pareja R, Manchanda R, Kosťun J, Dos Reis R, Meydanli MM, Odetto D, Laky R, Zapardiel I, Weinberger V, Benešová K, Borčinová M, Cardenas F, Wallin E, Pedone Anchora L, Akilli H, Abu-Rustum NR, Barquet-Muñoz SA, Javůrková V, Fischerová D and van Lonkhuijzen LRCW. Post-recurrence survival in patients with cervical cancer. Gynecol Oncol 2022; 164: 362-369.

[12] Xie R, Xie K, Lin X, Ji Y, Chen J and Chen C. A Comparison of neoadjuvant chemotherapy and concurrent chemoradiotherapy for for FIGO 2018 stage IB3/IIA2 Cervical squamous cell carcinoma: long-term efficacy and safety in a resource-limited setting. PLoS One 2025; 20: e0319405.

[13] Yang H, Huang SG, Dong M, Wang X, He J, Su H, Liu C, Zhu Y, Wei L and Liu Z. Efficacy and safety of bevacizumab in neoadjuvant and concurrent chemoradiotherapy for refractory cervical cancer patients. Biomol Biomed 2024; 24: 1586-1594.

[14] Jie S, Xiaoshuang F, Hao W, Changming Z, Miao M, Zezhou W, Jing Y, Xiaohua W and Ying Z. Metastasis patterns and survival analysis of 572 patients with metastatic cervical cancer: a hospital-based real world study. China oncoloy 2024; 34: 361-367.

[15] Finkel T, Serrano M and Blasco MA. The common biology of cancer and ageing. Nature 2007; 448: 767-74.

[16] Chen ACY, Jaiswal S, Martinez D, Yerinde C, Ji K, Miranda V, Fung ME, Weiss SA, Zschummel M, Taguchi K, Garris CS, Mempel TR, Hacohen N and Sen DR. The aged tumor microenvironment limits T cell control of cancer. Nat Immunol 2024; 25: 1033-1045.

[17] Berben L, Floris G, Wildiers H and Hatse S. Cancer and aging: two tightly interconnected biological processes. Cancers (Basel) 2021; 13: 1400.

[18] Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G and Vlastos AT. Prognostic value of histopathology and trends in cervical cancer: a SEER population study. BMC Cancer 2007; 7: 164.

[19] Jonska-Gmyrek J, Gmyrek L, Zolciak-Siwinska A, Kowalska M and Kotowicz B. Adenocarcinoma histology is a poor prognostic factor in locally advanced cervical cancer. Curr Med Res Opin 2019; 35: 595-601.

[20] Galic V, Herzog TJ, Lewin SN, Neugut AI, Burke WM, Lu YS, Hershman DL and Wright JD. Prognostic significance of adenocarcinoma histology in women with cervical cancer. Gynecol Oncol 2012; 125: 287-91.

[21] Taarnhøj GA, Christensen IJ, Lajer H, Fuglsang K, Jeppesen MM, Kahr HS and Høgdall C. Risk of recurrence, prognosis, and follow-up for Danish women with cervical cancer in 2005-2013: a national cohort study. Cancer 2018; 124: 943-951.

[22] Wang X, Shi W, Pu X, Hu Y, Chen R and Zhu H. Development and validation of nomograms to recurrence and survival in patients with early-stage cervical adenocarcinoma. J Cancer Res Clin Oncol 2023; 149: 13727-13739.

[23] Peiretti M, Zapardiel I, Zanagnolo V, Landoni F, Morrow CP and Maggioni A. Management of recurrent cervical cancer: a review of the literature. Surg Oncol 2012; 21: e59-66.

[24] Escande A, Gouy S, Mazeron R, Bentivegna E, Bacorro W, Maroun P, Schernberg A, Oberlander AS, Dumas I, Genestie C, Deutsch E, Morice P, Haie-Meder C and Chargari C. Outcome of early stage cervical cancer patients treated according to a radiosurgical approach: clinical results and prognostic factors. Gynecol Oncol 2017; 144: 541-546.

[25] Liu Y, Zhang N and Yang Q. Predicting the recurrence of usual-type cervical adenocarcinoma using a nomogram based on clinical and pathological factors: a retrospective observational study. Front Oncol 2024; 14: 1320265.