ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

ORIGINAL RESEARCH ARTICLE

Analysis of risk factors after three-dimensional brachytherapy for cervical cancer: A real-world study

Haonan Han[1,2†], Dongmin Liu[3†], Chengwu Zhang[4], Yuan Dong[1,2], Pan Qi[1,2], Siyang Zhang[1,2], Liming Xu[3,5*], and Xiaofeng Yao[1,2*]

[1]Department of Plastic Surgery, Xiangyang Hospital of Traditional Chinese Medicine, Xiangyang Hospital affiliated to Hubei University of Chinese Medicine, Xiangyang, Hubei, China

[2]Hubei Provincial Clinical Research Center for Integrative Medicine in Cancer Green Therapy, Xiangyang, Hubei, China

[3]Department of Radiation Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China

[4]Plastic Surgery Department, Third Xiangya Hospital of Central South University, Changsha, Hunan, China

[5]Department of Radiation Oncology, Tianjin Cancer Hospital Airport Hospital, Tianjin, China

[†]*These authors have contributed equally to this work.*

***Corresponding authors:**
Xiaofeng Yao (magicalyaoxiaofeng@foxmail.com);
Liming Xu (limingxu2008@gmail.com)

Citation: Han H, Liu D, Zhang C, *et al*. Analysis of risk factors after three-dimensional brachytherapy for cervical cancer: A real-world study. *Eurasian J Med Oncol.* doi: 10.36922/EJMO026080091

Received: February 20, 2026

Revised: April 29, 2026

Accepted: June 3, 2026

Published online: June 22, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

Introduction: Cervical cancer is a common malignancy of the female reproductive system. This study retrospectively analyzed cervical cancer patients treated with three-dimensional brachytherapy (3D-BT) to evaluate the effects of radiotherapy dose, treatment fractions, and combined therapeutic modalities on prognosis.

Objectives: To identify prognostic factors associated with treatment efficacy and provide evidence for individualized treatment strategies.

Methods: In this retrospective cohort study, data from cervical cancer patients treated with 3D-BT at Tianjin Cancer Hospital and Xiangyang Hospital of Traditional Chinese Medicine were collected. Variables included radiotherapy dose, treatment fractions, and combined treatment modalities. Kaplan–Meier and Cox regression analyses were performed using R and SPSS to identify prognostic factors associated with survival outcomes.

Results: Concurrent chemoradiotherapy, targeted therapy plus chemotherapy, targeted therapy plus hyperthermia, immunotherapy plus chemotherapy, immunotherapy plus hyperthermia, and hyperthermia plus chemotherapy were associated with improved progression-free survival (PFS) (all $p < 0.001$). Concurrent chemoradiotherapy (hazard ratio [HR]: 0.436, 95% confidence interval [CI]: 0.227–0.839, $p = 0.013$) and hyperthermia plus chemotherapy (HR: 0.106, 95% CI: 0.013–0.837, $p = 0.033$) were associated with reduced overall survival (OS) risk. A total brachytherapy dose > 2,800 cGy (HR: 0.177, 95% CI: 0.041–0.771, $p = 0.021$) and hyperthermia plus chemotherapy (HR: 0.186, 95% CI: 0.055–0.630, $p = 0.007$) were independently associated with improved PFS. More than four brachytherapy fractions were also associated with better PFS.

Conclusion: Higher brachytherapy doses (>2,800 cGy) and certain combination strategies, particularly concurrent chemoradiotherapy with hyperthermia, were associated with improved PFS and OS. However, the absence of key prognostic

variables limits interpretation, and prospective studies are required to confirm these findings.

Keywords: Cervical cancer; Three-dimensional brachytherapy; Radiotherapy; Prognostic correlates; Treatment modalities

1. Introduction

Cervical cancer is a common malignancy of the female reproductive system worldwide, especially in developing countries, where the incidence and mortality rates remain relatively high.[1–3] According to statistical data, the global annual incidence of cervical cancer is approximately 600,000 cases, with mortality rates remaining high. The incidence of cervical cancer increases significantly with age, particularly among women aged 40–60 years.[2] In recent years, with the advancement of screening technologies and vaccination programs[4,5], the early diagnosis rate of cervical cancer has improved[6], and the survival rate of patients with early-stage cervical cancer has been steadily increasing. However, despite these advancements, most cervical cancer patients still present at later stages, and the treatment outcomes for these patients remain a significant challenge.[7,8]

Three-dimensional brachytherapy (3D-BT) is a local radiation therapy technique that has made significant progress in the treatment of cervical cancer in recent years.[9,10] 3D-BT utilizes precise radiation planning and dose distribution to maximize tumor dose while minimizing radiation damage to surrounding normal tissues, significantly enhancing targeting and safety. Compared to traditional two-dimensional brachytherapy[11], 3D-BT has shown superior treatment efficacy and control of side effects, especially in improving local control rates and reducing complications. Currently, 3D-BT has become one of the essential treatment modalities for advanced cervical cancer patients, including for primary radiation therapy, postoperative adjuvant radiation therapy, and the treatment of recurrent cervical cancer.[12]

Despite the significant advantages of 3D-BT in cervical cancer treatment, particularly in enhancing tumor local control and reducing normal tissue damage, the use of 3D-BT alone may not achieve optimal therapeutic effects, especially in cases where the tumor has invaded surrounding or local tissues. As a result, in recent years, combined external irradiation (such as volumetric modulated arc therapy/intensity-modulated radiation therapy) with 3D-BT has gradually emerged as an important approach to improving treatment outcomes. This combined treatment approach can effectively expand the irradiation range of the tumor while precisely targeting the tumor site with 3D-BT, enhancing both the precision and effectiveness of the treatment, particularly in locally advanced cervical cancer patients. In addition to the combination of external irradiation and 3D-BT, other treatment modalities, such as targeted therapy, endocrine therapy, thermotherapy, and concurrent chemoradiotherapy (CRT), have also been widely applied and extensively studied in the clinical treatment of cervical cancer.[13–17] These therapies work synergistically through various mechanisms, further improving patient outcomes and providing more options for personalized treatment in clinical practice.

This study, based on extensive follow-up clinical data from the hospital's medical records system, draws on previous experience.[18] By conducting a retrospective analysis of the treatment approaches and processes of cervical cancer patients, the study aims to assess the impact of different treatment strategies on patient prognosis. Although the clinical application of 3D-BT has become increasingly refined, variations in radiation dose and fractionation schedules persist among physicians treating patients with various conditions.[19,20] How to optimize dosage, treatment frequency, and combined therapy strategies to maximize patient prognosis[21] remains an urgent issue that needs to be addressed. Through this retrospective analysis of clinical data, we aim to identify high-risk factors affecting prognosis and provide evidence to improve personalized clinical treatment.

2. Materials and methods

2.1. Study participants

The inclusion criteria for this study are: (i) Patients diagnosed with cervical cancer and receiving treatment at this hospital; (ii) Patients who have undergone 3D-BT; (iii) Patients with clear time points for each treatment session recorded; (iv) Patients who received combined treatments with clearly documented treatment protocols; (v) Patients with reliable and valid data.

The exclusion criteria are: (i) Patients diagnosed with non-cervical cancer; (ii) Patients with missing or incomplete data; (iii) Patients who explicitly refused to

participate in the study during follow-up.

This study includes 3D-BT patients diagnosed with cervical cancer at Tianjin Cancer Hospital and Xiangyang Hospital of Traditional Chinese Medicine up to July 2024. Relevant data were collected through the hospital information system, with a total of 681 patients initially enrolled. After excluding patients with missing, incomplete, or lost follow-up data (such as those not followed up during the COVID-19 pandemic), 636 patients remained. Based on the inclusion and exclusion criteria, 430 patients were ultimately included in the study.

2.2. Software and statistical methods

Data collection was performed using EpiData (version 3.1, EpiData Association, Denmark) for data programming and manual collection to establish the database. Statistical analyses were conducted using R software (v4.3.2, R Foundation for Statistical Computing, Austria) and Statistical Package for Social Sciences (SPSS 26.0, IBM, United States). Variables were grouped, and statistical analyses were performed using univariate and multivariate Cox regression analyses. Factors with a univariate p-value of <0.1 were included in multivariate analysis. Survival analysis was conducted using the Kaplan–Meier (K–M) method, with the primary outcomes being overall survival (OS) and progression-free survival (PFS). Before conducting multivariate Cox regression, multicollinearity among variables was assessed using variance inflation factors (VIFs); all variables in the final models had VIFs < 5, indicating that collinearity did not substantially affect the estimates. The proportional hazards assumption for the Cox models was tested using Schoenfeld residuals, and no significant violations were detected.

Of note, the total brachytherapy dose reported in this study refers to the physical prescription dose and does not include the contribution from external beam radiotherapy (EBRT), nor has it been converted to the equivalent dose in 2 Gy fractions (EQD2). This should be taken into consideration when interpreting the dose–response findings.

2.3. Treatment strategies and grouping

All treatment decisions for patients in this cohort were made by a multidisciplinary team based on the then-current National Comprehensive Cancer Network guidelines, the availability of therapeutic modalities, and individual patient characteristics (e.g., age, performance status, and comorbidities). No predetermined study-specific protocol was applied. For the purpose of comparing integrated treatment strategies, patients were additionally categorized into mutually exclusive groups according to the main combination they received: (i) CRT alone, (ii) CRT combined with hyperthermia, (iii) CRT combined with targeted therapy, (iv) CRT combined with immunotherapy, and (v) other combinations. These groups were used in K–M analysis to provide a more clinically interpretable comparison of major combination strategies.

3. Result

3.1. General population

Among the 430 patients, the average age was 57.39 (±10.794) years, with an age range of 23–84 years, all of whom were female. The average duration of brachytherapy was 23.56 (±12.448) days, with a total dose median of 2,800 cGy (ranging from 700 to 3,600 cGy), and the median number of fractions was four (ranging from one to seven). The median dose per fraction was 700 cGy, with a range from 400 to 750 cGy.

The average follow-up time was 16.727 (±12.881) months, with the shortest follow-up being 0.85 months and the longest reaching 89.86 months. The average progression-free follow-up time was 13.974 (±11.956) months, and the average OS follow-up time was 16.756 (±12.883) months. A total of 130 (30.2%) patients experienced disease progression, and 42 (9.8%) patients died. Other baseline characteristics are presented in Table 1.

3.2. Survival analysis

We conducted K–M survival analysis with OS and PFS as outcome events for cervical cancer patients undergoing 3D-BT. In the survival analysis with OS as the outcome event, no significant effects of radiotherapy-related and treatment-related factors on post-surgery OS were observed. However, in the survival analysis with PFS as the outcome event, we identified 10 factors that were associated with post-surgery PFS risk.

Regarding radiotherapy-related factors, receiving more than four fractions of brachytherapy (hazard ratio [HR] = 0.63, 95% confidence interval [CI]: 0.39–1.00, $p < 0.001$, Figure 1A) and a total dose greater than 2,800 cGy (HR = 0.56, 95% CI: 0.34–0.92, $p < 0.001$, Figure 1B) significantly improve PFS for cervical cancer patients undergoing 3D-BT. In terms of treatment-related factors, CRT (HR = 0.42, 95% CI: 0.28–0.62, $p < 0.001$, Figure 1C), targeted therapy combined with chemotherapy (HR = 0.56, 95% CI: 0.38–0.85, $p < 0.001$, Figure 1D), targeted therapy combined with hyperthermia (HR = 0.37, 95% CI: 0.18–0.77, $p < 0.001$, Figure 1E), immunotherapy combined with chemotherapy (HR = 0.50, 95% CI: 0.25–0.99, $p < 0.001$, Figure 1F), immunotherapy combined with

Table 1. Baseline characteristics of cervical cancer patients treated with three-dimensional brachytherapy

Variable	Subgroup	*n*	Percentage
Age (mean ± SD, range)	–	57.39 (±10.794)	23–84
Dose (cGy)	≤2,800	312	72.56
	>2,800	118	27.44
Fraction	≤4	311	72.33
	>4	119	27.67
cGy/f	≤700	427	99.30
	>700	3	0.70
Boost	No	408	94.88
	Yes	22	5.12
Interruption	No	311	72.33
	Yes	119	27.67
TT	No	323	75.12
	Yes	107	24.88
IT	No	363	84.42
	Yes	67	15.58
CRT	No	65	15.12
	Yes	365	84.88
Thermotherapy	No	249	57.91
	Yes	181	42.09
TT + IT	No	404	93.95
	Yes	26	6.05
TT + CRT	No	330	76.74
	Yes	100	23.26
IT + CRT	No	369	85.81
	Yes	61	14.19
Thermo + CRT	No	257	59.77
	Yes	173	40.23
Thermo + TT	No	390	90.70
	Yes	40	9.30
Thermo + IT	No	397	92.33
	Yes	33	7.67

Abbreviations: CRT: Concurrent chemoradiotherapy; IT: Immunotherapy; SD: Standard deviation; TT: Targeted therapy.

hyperthermia (HR = 0.50, 95% CI: 0.21–1.23, $p < 0.001$, Figure 1G), hyperthermia combined with chemotherapy (HR = 0.28, 95% CI: 0.17–0.45, $p < 0.001$, Figure 1H), and hyperthermia (HR = 0.28, 95% CI: 0.17–0.45, $p < 0.001$, Figure 1I) all had favorable effects on PFS prognosis in these patients. Additionally, although patients receiving a single dose greater than 700 cGy showed certain advantages in PFS prognosis compared to those receiving ≤ 700 cGy, the uneven distribution of outcome events precluded effective calculation of HR and 95% CI for this group. Further research is needed to obtain more data to support this finding.

The log-rank test revealed a statistically significant difference in PFS across the groups ($p < 0.001$). Pairwise comparisons indicated that patients receiving CRT combined with hyperthermia showed the most favorable

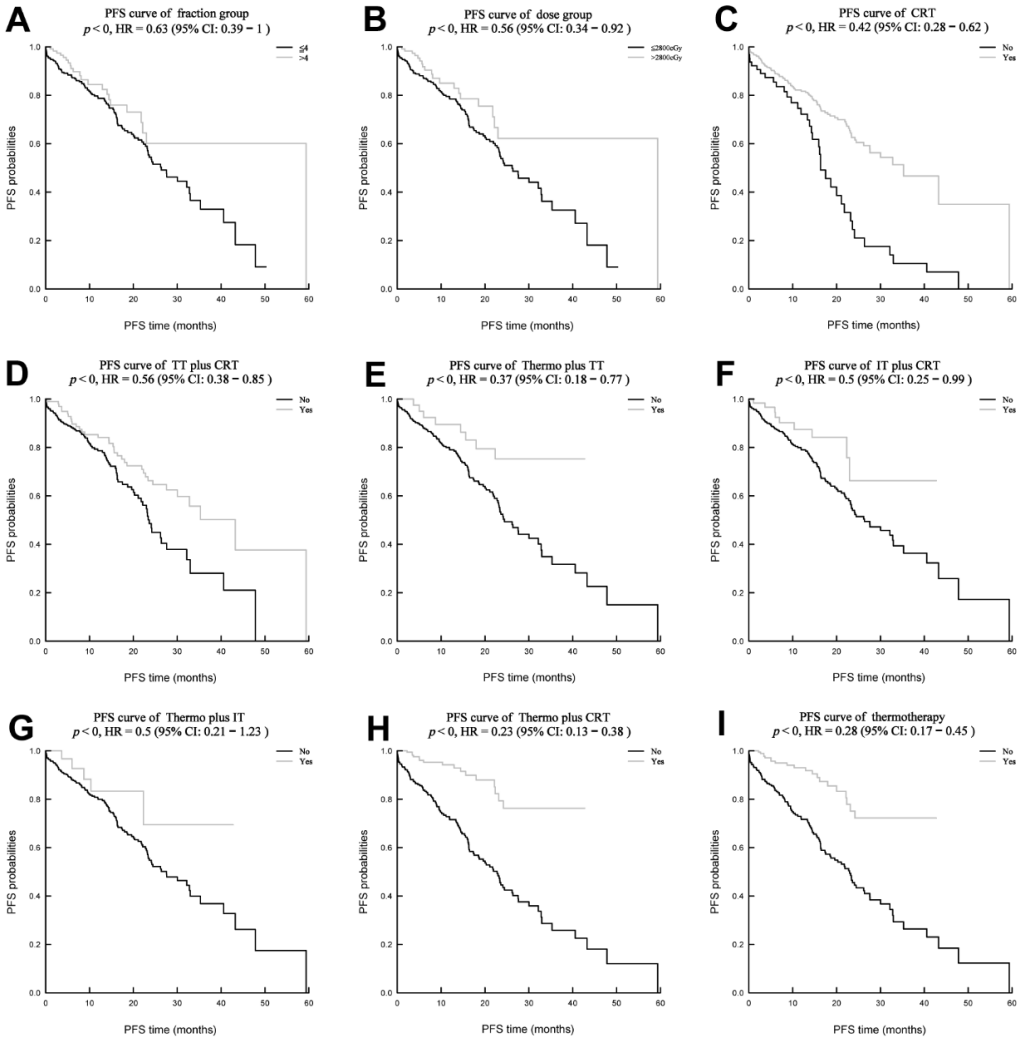


Figure 1. Impact of different factors on PFS in cervical cancer patients treated with three-dimensional brachytherapy
Abbreviations: CI: Confidence interval; CRT: Concurrent chemoradiotherapy; HR: Hazard ratio; IT: Immunotherapy; PFS: Progression-free survival; TT: Targeted therapy.

PFS, followed by those receiving CRT combined with immunotherapy. In contrast, patients receiving CRT alone exhibited the shortest median PFS. These descriptive results further support the potential benefit of integrating hyperthermia or immunotherapy with CRT in cervical cancer patients undergoing 3D-BT, although the non-randomized nature of this comparison precludes definitive conclusions.

3.3. Cox regression analysis

Univariate and multivariate analyses were conducted for the 430 cervical cancer patients with OS or PFS as outcome events. A total of 15 related factors were analyzed. In the univariate COX analysis for OS, four factors were included in the multivariate analysis: CRT, hyperthermia, immunotherapy combined with chemotherapy, and hyperthermia combined with chemotherapy. In the univariate Cox analysis for PFS, 10 factors were included in the multivariate analysis: dose group (cGy), fraction group (times), targeted therapy, CRT, hyperthermia, targeted therapy combined with chemotherapy, immunotherapy combined with chemotherapy, hyperthermia combined with chemotherapy, targeted therapy combined with hyperthermia, and immunotherapy combined with hyperthermia (Tables 2 and 3).

Table 2. Univariate Cox regression analysis

Variable	Subgroup	OS univariate				PFS univariate			
		HR	95% CI (low–high)		*p*	HR	95% CI (low–high)		*p*
Dose (cGy)	≤2,800	Ref.				Ref.			
	>2,800	0.519	0.203	1.325	0.170	0.618	0.387	0.988	0.045
Fraction	≤4	Ref.				Ref.			
	>4	0.761	0.337	1.719	0.511	0.683	0.435	1.075	0.099
cGy/f	≤700	Ref.				Ref.			
	>700	0.998	0.993	1.002	0.310	0.998	0.995	1.001	0.245
Boost	No	Ref.				Ref.			
	Yes	0.000	0.000	0.000	0.997	0.833	0.306	2.265	0.720
Interruption	No	Ref.				Ref.			
	Yes	0.826	0.366	1.862	0.645	1.316	0.882	1.963	0.179
TT	No	Ref.				Ref.			
	Yes	0.620	0.318	1.210	0.161	0.718	0.489	1.053	0.090
IT	No	Ref.				Ref.			
	Yes	0.519	0.160	1.686	0.275	0.715	0.417	1.227	0.223
CRT	No	Ref.				Ref.			
	Yes	0.271	0.146	0.504	0.000	0.451	0.306	0.663	0.000
Thermotherapy	No	Ref.				Ref.			
	Yes	0.223	0.079	0.629	0.005	0.276	0.171	0.445	0.000
TT + IT	No	Ref.				Ref.			
	Yes	0.689	0.166	2.858	0.608	1.004	0.509	1.981	0.990
TT + CRT	No	Ref.				Ref.			
	Yes	0.559	0.278	1.123	0.102	0.642	0.432	0.955	0.029
IT + CRT	No	Ref.				Ref.			
	Yes	0.185	0.025	1.344	0.095	0.452	0.229	0.891	0.022
Thermo + CRT	No	Ref.				Ref.			
	Yes	0.112	0.027	0.465	0.003	0.225	0.133	0.381	0.000
Thermo + TT	No	Ref.				Ref.			
	Yes	0.320	0.077	1.327	0.116	0.393	0.192	0.807	0.011
Thermo + IT	No	Ref.				Ref.			
	Yes	0.663	0.160	2.750	0.571	0.418	0.171	1.025	0.057

Abbreviations: CI: Confidence interval; CRT: Concurrent chemoradiotherapy; HR: Hazard ratio; IT: Immunotherapy; OS: Overall survival; PFS: Progression-free survival; TT: Targeted therapy.

Table 3. Multivariate Cox regression analysis

Variable	Subgroup	OS multivariate				PFS multivariate			
		HR	95% CI (low–high)		*p*	HR	95% CI (low–high)		*p*
Dose (cGy)	≤2,800					Ref.			
	>2,800					0.177	0.041	0.771	0.021
Fraction	≤4					Ref.			
	>4					3.194	0.772	13.221	0.109
TT	No					Ref.			
	Yes					1.152	0.415	3.203	0.786
CRT	No	Ref.				Ref.			
	Yes	0.436	0.227	0.839	0.013	0.938	0.587	1.500	0.790
Thermotherapy	No	Ref.				Ref.			
	Yes	1.589	0.361	6.999	0.541	0.917	0.294	2.860	0.881
TT + CRT	No					Ref.			
	Yes					0.553	0.185	1.651	0.288
IT + CRT	No	Ref.				Ref.			
	Yes	0.370	0.049	2.764	0.332	0.560	0.239	1.310	0.181
Thermo + CRT	No	Ref.				Ref.			
	Yes	0.106	0.013	0.837	0.033	0.186	0.055	0.630	0.007
Thermo + TT	No					Ref.			
	Yes					1.833	0.642	5.235	0.258
Thermo + IT	No					Ref.			
	Yes					2.069	0.558	7.670	0.277

Abbreviations: CI: Confidence interval; CRT: Concurrent chemoradiotherapy; HR: Hazard ratio; IT: Immunotherapy; OS: Overall survival; PFS: Progression-free survival; TT: Targeted therapy.

Multivariate analysis showed that CRT (HR: 0.436, 95% CI: 0.227–0.839, p = 0.013) and hyperthermia combined with chemotherapy (HR: 0.106, 95% CI: 0.013–0.837, p = 0.033) were significantly associated with reduced OS risk in cervical cancer patients undergoing 3D-BT.

The dose group greater than 2,800 cGy (HR: 0.177, 95% CI: 0.041–0.771, p = 0.021) and hyperthermia combined with chemotherapy (HR: 0.186, 95% CI: 0.055–0.630, p = 0.007) were independently associated with improved PFS in cervical cancer patients undergoing 3D-BT.

3.4. Nomogram prediction model and evaluation

We developed a nomogram prediction model for cervical cancer patients undergoing 3D-BT, with PFS as the outcome, using factors such as dose, fractionation, and combined treatment methods. The model predicts the 2-year, 3-year, and 5-year PFS probabilities. A random split of the data was performed, with 70% used for model development and 30% for internal validation. The prediction model was successfully established in the development group (Figure 2), with a C-index of 0.708, indicating moderate predictive ability, and a C-index of 0.704 in the internal validation group, demonstrating similar predictive performance. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were also assessed. The AUC values for 2 years (AUC = 0.689), 3 years (AUC = 0.727), and 5 years (AUC = 0.723) all demonstrated remarkable performance (Figure 3).

Calibration plots for 2-year, 3-year, and 5-year PFS predictions demonstrated acceptable agreement between predicted and observed outcomes in the internal validation

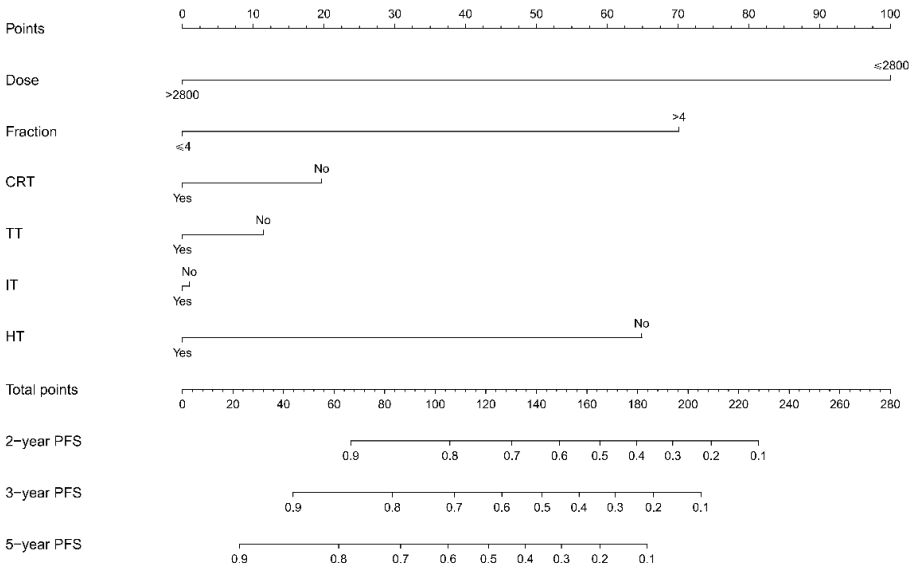


Figure 2. Nomogram prediction model for PFS in cervical cancer three-dimensional brachytherapy patients
Abbreviations: CRT: Concurrent chemoradiotherapy; HT: Hyperthermia; IT: Immunotherapy; PFS: Progression-free survival; TT: Targeted therapy.

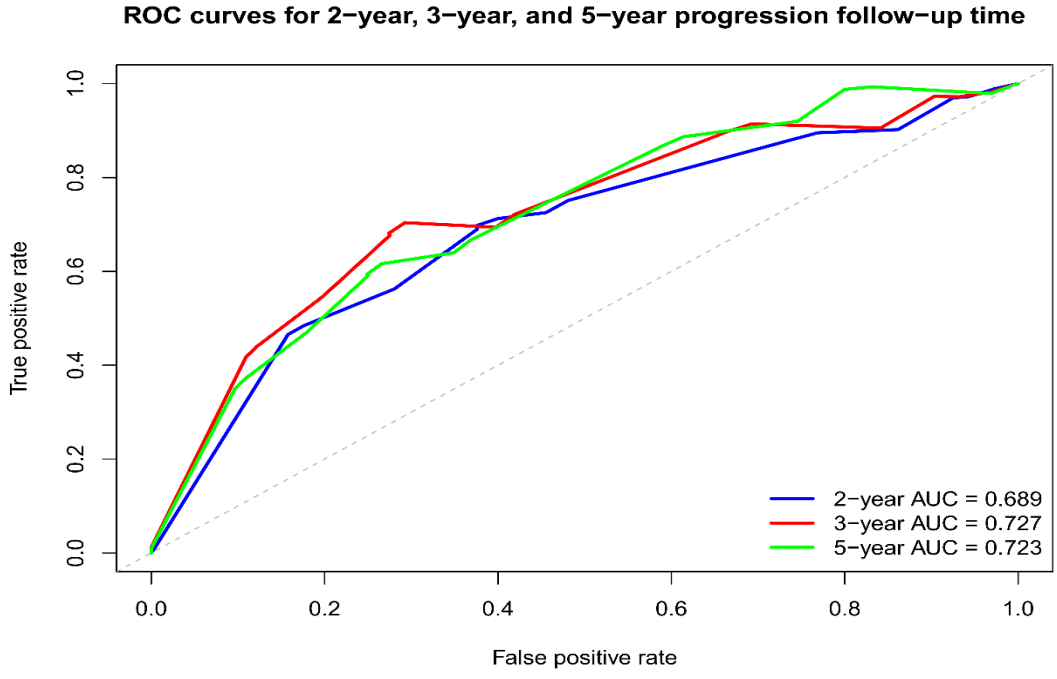


Figure 3. Receiver operating characteristic curve validation of the prediction model
Abbreviation: AUC: Area under the curve.

set (Figure 4A–4C). However, external validation is lacking, and the nomogram should be regarded as an exploratory tool rather than a ready-to-use clinical instrument.

4. Discussion

In the clinical treatment of cervical cancer, we found that CRT and hyperthermia combined with chemotherapy are key factors associated with the OS risk for cervical cancer patients undergoing 3D-BT. Additionally, a total treatment dose exceeding 2,800 cGy and hyperthermia combined with chemotherapy showed significant clinical benefits in reducing the risk of PFS.

Regarding radiotherapy-related factors, we identified that treatment with more than four brachytherapy fractions and a total dose exceeding 2,800 cGy were independent factors that significantly improved PFS in cervical cancer patients undergoing 3D-BT. This suggests that the total radiation dose and the number of fractions play a crucial role in extending patients' PFS.[12,19,22]

In terms of treatment strategies, we observed that CRT, targeted therapy combined with chemotherapy, targeted therapy combined with hyperthermia, immunotherapy combined with chemotherapy, immunotherapy combined with hyperthermia, hyperthermia combined with chemotherapy, and chemotherapy combined with hyperthermia all had favorable effects on PFS in patients undergoing 3D-BT. These combined treatment approaches, by integrating diverse therapeutic modalities and mechanisms, may effectively delay tumor progression and improve patients' quality of life. Particularly when combined with hyperthermia and chemotherapy, these strategies enhance tumor cell radiosensitivity and boost the immune system's anti-tumor response, further strengthening the treatment effect.

These findings suggest that treatment intensity and combination modality may play a clinically meaningful role in patient outcomes. However, the optimal dose, fractionation, and combination regimen cannot be determined from this retrospective analysis and should be investigated in future prospective studies that incorporate complete staging information.

Additionally, we established a nomogram that provides forward-looking PFS predictions based on clinical treatment-related factors in cervical cancer patients undergoing 3D-BT. By incorporating factors such as dose, fractionation, and combined treatment, this model offers valuable prognostic insights, thus better guiding the application of clinical treatment strategies.

In the clinical treatment of cervical cancer, 3D-BT has become an important radiotherapy modality. With the continuous advancement of medical technology, the effectiveness of 3D-BT has significantly improved, especially when combined with other therapeutic strategies, resulting in more pronounced clinical benefits. The development of 3D-BT has been particularly notable, driven by advances in radiotherapy technology, especially the rapid development of computers, artificial intelligence, and imaging technologies. Early brachytherapy relied mainly on two-dimensional imaging and simpler treatment planning, which often led to standard target areas and lower accuracy. However, with the widespread application of imaging technologies such as computed tomography and magnetic resonance imaging, 3D-BT has been able to provide more accurate tumor target localization[22,23], resulting in more precise and uniform dose delivery, thereby reducing damage to surrounding healthy tissues. This technological advancement has significantly improved the local control rate and quality of life for cervical cancer patients.[11] Studies have shown that with appropriate dosage and fractionation schemes, 3D-BT can significantly prolong patients' PFS and OS, making it widely applied in clinical treatment.[24]

Concurrent chemoradiotherapy is a standard treatment protocol for cervical cancer, where radiotherapy and chemotherapy work synergistically through different mechanisms. Radiotherapy primarily works by damaging tumor cell DNA through radiation, inhibiting tumor growth, while chemotherapy drugs directly kill cancer cells or inhibit their proliferation. The combination of CRT and 3D-BT can enhance the overall treatment effect. Research has shown that the combination of CRT and 3D-BT in clinical treatment for cervical cancer can significantly improve the local control rate and prolong both PFS and OS.[25]

Hyperthermia, as an adjunctive therapy, has demonstrated potential to enhance the effects of radiotherapy across multiple cancer types. Hyperthermia works by locally heating the tumor, increasing tumor cell radiosensitivity, and thereby enhancing the efficacy of radiotherapy. Combining hyperthermia with 3D-BT in the treatment of cervical cancer can improve treatment outcomes by enhancing the radiosensitivity of tumor cells and boosting immune responses.[17] Studies have shown that the combination of hyperthermia and 3D-BT effectively delays the progression of cervical cancer, with relatively mild side effects, making it a promising combination therapy strategy.[26,27]

Targeted therapy and immunotherapy have become hot topics in cancer treatment research in recent years. Targeted therapy works by specifically targeting tumor cell molecules, inhibiting tumor growth[28–30], whereas immunotherapy

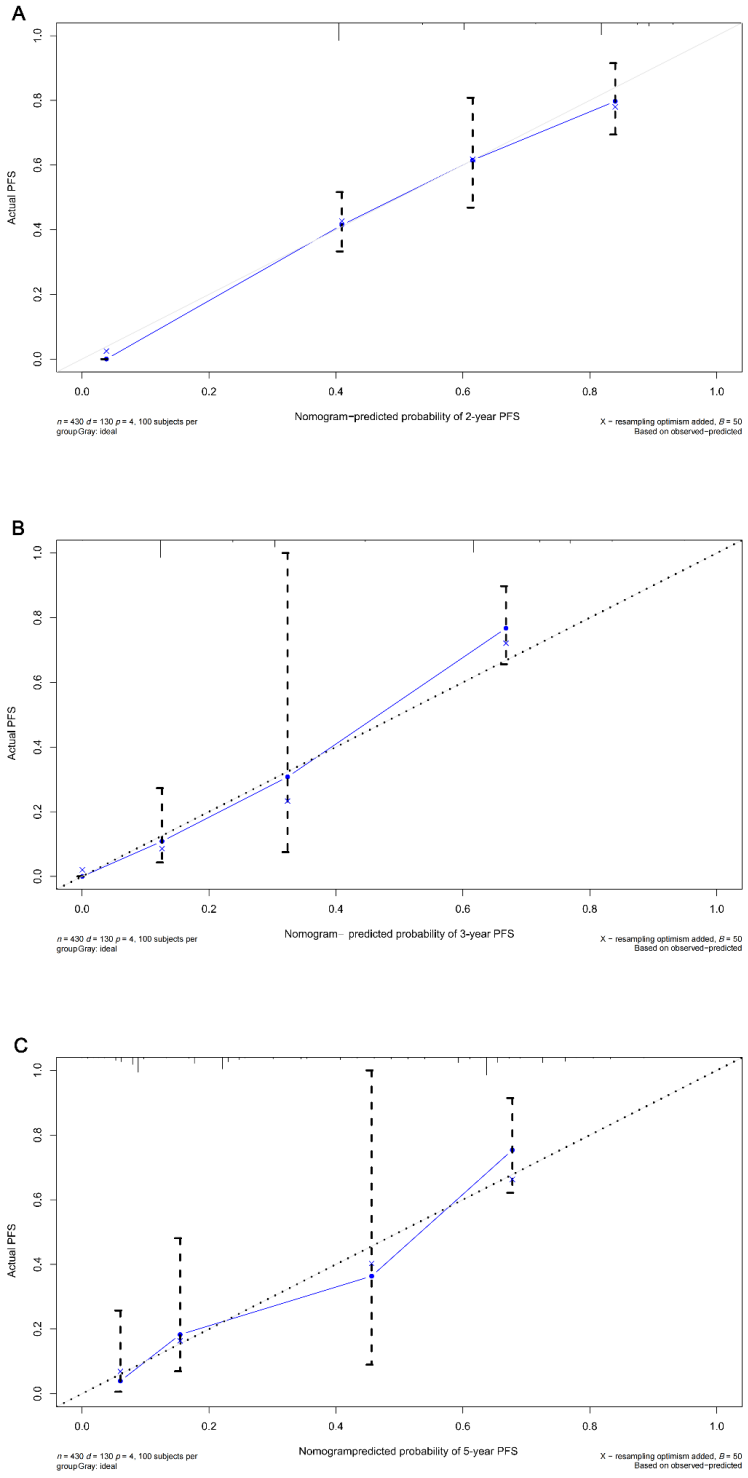


Figure 4. Calibration curves for nomogram-predicted probability of 2-, 3-, and 5-year PFS
Abbreviation: PFS: Progression-free survival.

enhances the body's immune response against cancer by activating the immune system.[31–33] Combining targeted therapy with 3D-BT enables the synergistic effects of radiotherapy and molecular targeted therapy, improving the precision and efficacy of treatment.[34] At the same time, combining immunotherapy with 3D-BT improves the body's immune response, reduces tumor immune escape, and enhances the efficacy of radiotherapy.[35,36]

This growing body of evidence supports the importance of combining 3D-BT with other therapeutic modalities, including chemotherapy, hyperthermia, targeted therapy, and immunotherapy, to improve clinical outcomes and patient survival in cervical cancer treatment.

This study has several important limitations that must be acknowledged. First and most critically, the analysis does not include key prognostic variables such as the International Federation of Gynecology and Obstetrics stage, tumor size, lymph node status, histological subtype, and performance status. These factors are well-established determinants of survival in cervical cancer, and their absence introduces substantial unmeasured confounding. The treatment-associated factors identified here may therefore be confounded by differences in disease severity, and the reported independent associations should be interpreted cautiously as they may change materially if these staging variables were available for adjustment. Second, the number of death endpoint events included in the study was small (42 deaths), and the median follow-up was relatively short (~17 months), which may partly reflect the relatively recent implementation of 3D-BT in clinical practice. Consequently, the OS-related analyses are underpowered and must be regarded as preliminary. Third, the data were not stratified by key clinical characteristics due to insufficient follow-up data and the absence of valid stratification factors in the current dataset. Moving forward, we will continue standardized follow-up, aim to collect complete staging and toxicity data, and refer to other clinical studies to propose meaningful stratification factors for further validation of survival and progression outcomes in different subgroups. Fourth, treatment-related toxicity data were not systematically documented in the institutional records and therefore could not be analyzed in this study. This is a recognized limitation of retrospective real-world studies, and prospective collection of graded adverse events will be a key objective of our future research. Fifth, the brachytherapy dose threshold reported herein refers to the physical dose only and was not converted to EQD2, nor does it account for the EBRT contribution. This limits the biological interpretability and cross-study comparability of the dose threshold.

Importantly, although our analyses revealed multiple treatment components that are independently associated with improved PFS or OS, this retrospective design cannot identify a single "best" combined regimen. The choice of combination therapy in real-world practice is influenced by numerous clinical and non-clinical factors, which are likely to introduce selection bias. The supplementary comparison of integrated strategies is intended to visually illustrate outcome trends, but it does not replace formal comparative effectiveness research. Well-designed prospective trials are needed to determine the optimal therapeutic sequence and combination for cervical cancer patients receiving 3D-BT.

With the continuous advancement of medical technology, the treatment methods and combination therapy strategies for cervical cancer using 3D-BT will also continue to innovate. In the future, we aim to improve the precision and effectiveness of 3D-BT through the development of precision medicine, the integration of new immunotherapy approaches, and ongoing technological innovations. By combining 3D-BT with other treatment modalities, we hope to provide patients with more diverse and effective treatment options. This will maximize the potential of brachytherapy, helping patients achieve better treatment outcomes and improved quality of life.

5. Conclusion

This real-world study demonstrated that treatment-related factors play an important role in the prognosis of cervical cancer patients receiving 3D-BT. A total brachytherapy dose exceeding 2,800 cGy and intensified combination strategies, particularly concurrent chemoradiotherapy and hyperthermia-based regimens, were associated with favorable survival outcomes. In addition, a greater number of brachytherapy fractions showed a potential benefit for progression-free survival.

These findings suggest that optimizing radiation dose and integrating multimodal therapies may further improve the efficacy of 3D-BT and provide valuable information for individualized treatment planning in cervical cancer. However, because of the retrospective nature of this study and the absence of several key prognostic variables, the observed associations should be interpreted with caution. Prospective studies with longer follow-up and more comprehensive clinical data are warranted to validate these findings and to determine the optimal treatment strategies for patients undergoing 3D-BT.

Acknowledgments

None.

Funding

This study is funded by Demonstration Project 2025 for

Reform and High-Quality Development of National Public Hospitals (Informal Letter for Public Hospital Reform and Department of Institutional Reform, National Health Commission of the People's Republic of China [2025] No. 3).

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Haonan Han, Xiaofeng Yao, Liming Xu
Formal analysis: Haonan Han, Chengwu Zhang, Yuan Dong, Pan Qi, Siyang Zhang
Investigation: Dongmin Liu, Chengwu Zhang, Yuan Dong, Pan Qi, Siyang Zhang
Methodology: Haonan Han, Dongmin Liu
Writing–original draft: Haonan Han
Writing–review & editing: Dongmin Liu, Chengwu Zhang

Ethics approval and consent to participate

The study was approved by the Human Investigation Committee of Tianjin Medical University Cancer Hospital (approval ID: bc20240420) and the Ethics Committee of Xiangyang Hospital of Traditional Chinese Medicine (Xiangyang Institute of Traditional Chinese Medicine) (approval ID: 2026-033). This is a retrospective study using de-identified data from the hospital information system. The requirement for informed consent was waived by the ethics committees of Tianjin Medical University Cancer Hospital and Xiangyang Hospital of Traditional Chinese Medicine.

Consent for publication

This study is a retrospective analysis using de-identified data. A waiver of informed consent was applied for and approved; therefore, consent was not required. All real names, ID numbers, and other identifiers have been kept strictly confidential.

Availability of data

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Ngu SF, Cheung ANY, Jong KK, *et al.* 2024 Hong Kong College of Obstetricians and Gynaecologists Guidelines for cervical cancer prevention and screening. *Hong Kong Med J*. 2024;

   doi: 10.12809/hkmj2411547

2. Abu-Rustum NR, Yashar CM, Arend R, *et al.* NCCN Guidelines® Insights: Cervical Cancer, Version 1.2024. *J Natl Compr Cancer Netw.* 2023;21(12):1224-1233.

   doi: 10.6004/jnccn.2023.0062

3. Vu M, Yu J, Awolude OA, Chuang L. Cervical cancer worldwide. *Curr Probl Cancer.* 2018;42(5):457-465.

   doi: 10.1016/j.currproblcancer.2018.06.003

4. Grce M, Musa J, Achenbach CJ, *et al.* Effect of cervical cancer education and provider recommendation for screening on screening rates: A systematic review and meta-analysis. *PLoS ONE.* 2017;12(9):e0183924.

   doi: 10.1371/journal.pone.0183924

5. Lei J, Ploner A, Elfström KM, *et al.* HPV Vaccination and the Risk of Invasive Cervical Cancer. *New Engl J Med*. 2020;383(14):1340-1348.

   doi: 10.1056/NEJMoa1917338

6. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. *Syst Rev.* 2013;2(1).

   doi: 10.1186/2046-4053-2-35

7. Vieira-Serna S, Viveros-Carreño D, Rodríguez J, *et al.* Preoperative brachytherapy for early-stage cervical cancer: Systematic review and meta-analysis. *Gynecol Oncol.* 2023;169:4-11.

   doi: 10.1016/j.ygyno.2022.11.009

8. Castelnau-Marchand P, Chargari C, Haie-Meder C, Mazeron R. Image-guided adaptive brachytherapy in locally advanced cervical cancer: recent advances and perspectives. *Curr Opin Oncol.* 2016;28(5):419-428.

   doi: 10.1097/cco.0000000000000309

9. Li F, Lu S, Zhao H, Mu X, Mao Z. Three-dimensional image-guided combined intracavitary and interstitial high-dose-rate brachytherapy in cervical cancer: A systematic review. *Brachytherapy*. 2021;20(1):85-94.

   doi: 10.1016/j.brachy.2020.08.007

10. Mendez LC, Weiss Y, D'Souza D, Ravi A, Barbera L, Leung E. Three-dimensional-guided perineal-based interstitial brachytherapy in cervical cancer: A systematic review of technique, local control and toxicities. *Radiother Oncol.* 2017;123(2):312-318.

    doi: 10.1016/j.radonc.2017.03.005

11. Suzumura EA, Gama LM, Jahn B, Campolina AG, Carvalho HdA, de Soárez PC. Effects of 3D image-guided brachytherapy compared to 2D conventional brachytherapy on clinical outcomes in patients with cervical cancer: A systematic review and meta-analyses. *Brachytherapy*. 2021;20(4):710-737.

    doi: 10.1016/j.brachy.2021.03.004

12. Tang X, Mu X, Zhao Z, Zhao H, Mao Z. Dose–effect response in image-guided adaptive brachytherapy for cervical cancer: A systematic review and meta-regression analysis. *Brachytherapy*. 2020;19(4):438-446.

doi: 10.1016/j.brachy.2020.02.012

13. Horeweg N, Mittal P, Gradowska PL, Boere I, Chopra S, Nout RA. Adjuvant Systemic Therapy after Chemoradiation and Brachytherapy for Locally Advanced Cervical Cancer: A Systematic Review and Meta-Analysis. *Cancers*. 2021;13(8):1880.

doi: 10.3390/cancers13081880

14. Kilic C, Kimyon Comert G, Cakir C, *et al.* Recurrence pattern and prognostic factors for survival in cervical cancer with lymph node metastasis. *J Obstet Gynaecol Res.* 2021;47(6):2175-2184.

doi: 10.1111/jog.14762

15. Gadducci A, Cosio S. Neoadjuvant Chemotherapy in Locally Advanced Cervical Cancer: Review of the Literature and Perspectives of Clinical Research. *Anticancer Res*. 2020;40(9):4819-4828.

doi: 10.21873/anticanres.14485

16. Ferrall L, Lin KY, Roden RBS, Hung C-F, Wu TC. Cervical Cancer Immunotherapy: Facts and Hopes. *Clin Cancer Res*. 2021;27(18):4953-4973.

doi: 10.1158/1078-0432.Ccr-20-2833

17. Van Der Zee J, Van Rhoon GC. Cervical cancer: Radiotherapy and hyperthermia. *Int J Hyperthermia*. 2009;22(3):229-234.

doi: 10.1080/02656730600722578

18. Han H, Hou H, Qiu L, *et al.* Evaluating the impact of brachytherapy duration on therapeutic outcomes in patients with cervical cancer. *ARNM*. 2024;2(4):4310.

doi: 10.36922/arnm.4310

19. Tanderup K, Nesvacil N, Kirchheiner K, *et al.* Evidence-Based Dose Planning Aims and Dose Prescription in Image-Guided Brachytherapy Combined With Radiochemotherapy in Locally Advanced Cervical Cancer. *Semin Radiat Oncol.* 2020;30(4):311-327.

doi: 10.1016/j.semradonc.2020.05.008

20. Sturdza AE, Knoth J. Image-guided brachytherapy in cervical cancer including fractionation. *Int J Gynecol Cancer.* 2022;32(3):273-280.

doi: 10.1136/ijgc-2021-003056

21. Schmid MP, Lindegaard JC, Mahantshetty U, *et al.* Risk Factors for Local Failure Following Chemoradiation and Magnetic Resonance Image–Guided Brachytherapy in Locally Advanced Cervical Cancer: Results From the EMBRACE-I Study. *J Clin Oncol*. 2023;41(10):1933-1942.

doi: 10.1200/jco.22.01096

22. Kim Y, Modrick JM, Pennington EC, Kim Y. Commissioning of a 3D image-based treatment planning system for high-dose-rate brachytherapy of cervical cancer. *J Appl Clin Med Phys.* 2016;17(2):405-426.

doi: 10.1120/jacmp.v17i2.5818

23. Goyal MK, Rai DV, Kehwar TS, *et al.* Anatomy-based definition of point A utilizing three-dimensional volumetric imaging approach for high-dose-rate (HDR) intracavitary brachytherapy dose prescription when treating cervical cancer using limited resources. *J Appl Clin Med Phys.* 2016;17(6):69-77.

doi: 10.1120/jacmp.v17i6.6029

24. Pötter R, Haie-Meder C, Limbergen EV, *et al.* Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol.* 2006;78(1):67-77.

doi: 10.1016/j.radonc.2005.11.014

25. Delgado D, Figueiredo A, Mendonça V, Jorge M, Abdulrehman M, de Pina M. Results from chemoradiotherapy for squamous cell cervical cancer with or without intracavitary brachytherapy. *J Contemp Brachytherapy.* 2019;11(5):417-422.

doi: 10.5114/jcb.2019.88116

26. Jiang P, Wei S, Bai Y, *et al.* The Efficacy of Volumetric Modulated Arc Therapy Combined With Chemotherapy, Brachytherapy, and Local Hyperthermia on Patients with Locally Advanced Cervical Cancer: A Retrospective Study. *Technol Cancer Res Treat.* 2023;22.

doi: 10.1177/15330338231185013

27. Saito T, Murakami M, Sumiya T, *et al.* Multimodal treatment with chemoradiotherapy, regional hyperthermia and interstitial brachytherapy for a huge locally advanced cervical cancer: A case report. *Tech Innov Patient Support Radiat Oncol.* 2023;28:100222.

doi: 10.1016/j.tipsro.2023.100222

28. Kunnummal M, Angelin M, Das AV. PIWI proteins and piRNAs in cervical cancer: a propitious dart in cancer stem cell-targeted therapy. *Human Cell.* 2021;34(6):1629-1641.

doi: 10.1007/s13577-021-00590-4

29. Ghosh S, Jayaram P, Kabekkodu SP, Satyamoorthy K. Targeted drug delivery in cervical cancer: Current perspectives. *Eur J Pharmacol.* 2022;917:174751.

doi: 10.1016/j.ejphar.2022.174751

30. Ye H, Chu X, Cao Z, *et al.* A Novel Targeted Therapy System for Cervical Cancer: Co-Delivery System of Antisense LncRNA of MDC1 and Oxaliplatin Magnetic

Thermosensitive Cationic Liposome Drug Carrier. *Int J Nanomed.* 2021;16:1051-1066.

doi: 10.2147/ijn.S258316

31. Monk BJ, Enomoto T, Kast WM, *et al.* Integration of immunotherapy into treatment of cervical cancer: Recent data and ongoing trials. *Cancer Treat Rev.* 2022;106:102385.

doi: 10.1016/j.ctrv.2022.102385

32. Yu L, Lanqing G, Huang Z, *et al.* T cell immunotherapy for cervical cancer: challenges and opportunities. *Front Immunol.* 2023;14.

doi: 10.3389/fimmu.2023.1105265

33. Gutiérrez-Hoya A, Soto-Cruz I. NK Cell Regulation in Cervical Cancer and Strategies for Immunotherapy. *Cells*. 2021;10(11):3104.

doi: 10.3390/cells10113104

34. Feng CH, Mell LK, Sharabi AB, McHale M, Mayadev JS. Immunotherapy With Radiotherapy and Chemoradiotherapy for Cervical Cancer. *Semin Radiat Oncol.* 2020;30(4):273-280.

doi: 10.1016/j.semradonc.2020.05.003

35. Yao S, Zhao L, Chen S, *et al.* Cervical cancer immune infiltration microenvironment identification, construction of immune scores, assisting patient prognosis and immunotherapy. *Front Immunol.* 2023;14.

doi: 10.3389/fimmu.2023.1135657

36. Sherer MV, Kotha NV, Williamson C, Mayadev J. Advances in immunotherapy for cervical cancer: recent developments and future directions. *Int J Gynecol Cancer.* 2022;32(3):281-287.

doi: 10.1136/ijgc-2021-002492