

ORIGINAL ARTICLE

Temporal changes in the delivery of definitive chemoradiotherapy for locally advanced cervical cancer: a retrospective single-center study

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Submitted: 02 May 2026

Revised: 03 July 2026

Accepted: 09 July 2026

Online First: 16 July 2026



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Summary

Introduction: Patients with locally advanced cervical cancer (LACC) are commonly treated with definitive chemoradiotherapy (CRT), consisting of external beam radiotherapy (EBRT), concurrent chemotherapy, and brachytherapy. Advances in radiotherapy techniques and imaging over the past decade have led to important changes in treatment delivery. This study aimed to evaluate temporal changes in CRT delivery in patients with LACC.

Methods: This retrospective single-center cohort study included 200 patients with LACC treated with definitive CRT at the Institute for Oncology and Radiology of Serbia. Two cohorts were analyzed: 100 patients treated in 2010–2011 and 100 patients treated in 2022–2023. Clinical and treatment-related parameters, including chemotherapy administration, EBRT technique, dose and fractionation, brachytherapy characteristics, and baseline patient characteristics, were compared.

Results: Significant differences were observed between the two cohorts. The use of concurrent chemotherapy and the number of administered cycles differed significantly between the two cohorts ($p < 0.001$). A complete transition from conventional radiotherapy techniques to IMRT/VMAT was observed in the later period ($p < 0.001$), along with the introduction of simultaneous integrated boost (SIB). Differences were also identified in EBRT fractionation and total dose ($p < 0.001$). In brachytherapy, significant variations in dose and fractionation were observed ($p < 0.001$ and $p < 0.05$), while applicator type remained comparable.

Conclusion: Significant temporal changes in CRT delivery were observed, reflecting the adoption of modern radiotherapy techniques and evolving treatment strategies. These findings indicate increasing treatment individualization and greater use of contemporary radiotherapy approaches in routine clinical practice within a middle-income setting.

Keywords: cervical cancer, chemoradiotherapy, IMRT, brachytherapy, radiotherapy techniques

INTRODUCTION

Cervical cancer remains a significant global health problem and one of the leading causes of cancer-related morbidity and mortality among women worldwide, particularly in low- and middle-income countries (1,2). According to recent global estimates, over 660,000 new cases and approximately 350,000 deaths were reported in 2022, reflecting the substantial burden of this largely preventable disease (1). Despite advances in prevention, including organized screening programs and human papillomavirus (HPV) vaccination, marked disparities persist between high-income and low-resource settings (2).

In high-income countries, a high coverage of the population with HPV vaccination and the implementation of effective screening strategies have led to a substantial decline in both incidence and mortality rates. In contrast, many countries in Central and Eastern Europe continue to report relatively high incidence rates, particularly in patients with locally advanced disease, indicating ongoing challenges in early detection and access to healthcare services (1,2). Serbia is among the highest-burden countries in this region. According to data from the Serbian Cancer Registry, 1,048 new cases of cervical cancer were reported in 2024, corresponding to a crude incidence rate of approximately 31.0 per 100,000 women, highlighting the continued public health importance of this disease at the national level (3).

Locally advanced cervical cancer (LACC), most commonly defined as FIGO stages IIB–IVA, represents a substantial proportion of newly diagnosed cases and is associated with a less favorable prognosis compared with early-stage disease (4,5). For these patients, definitive chemoradiotherapy (CRT), consisting of external beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy, remains the standard of care (5,6).

Over the past decade, important advances in radiotherapy planning and delivery have transformed the management of LACC. The transition from conventional two-dimensional and three-dimensional conformal radiotherapy techniques to intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and image-guided radiotherapy (IGRT) has enabled improved target coverage and sparing of surrounding normal tissues (7–10). In parallel, developments in image-guided brachytherapy and treatment planning have further refined treatment delivery (11,12).

Figures 1–7 illustrate representative examples of the evolution of radiotherapy techniques for locally advanced cervical cancer over the past decade. Figure 1 demonstrates conventional two-dimensional external beam radiotherapy (2D-EBRT). Figures 2 and 3 compare three-dimensional conformal radiotherapy (3D-CRT) using the four-field box technique and modern volumetric modulated arc therapy (VMAT), illustrating the improved dose conformity and superior sparing of organs

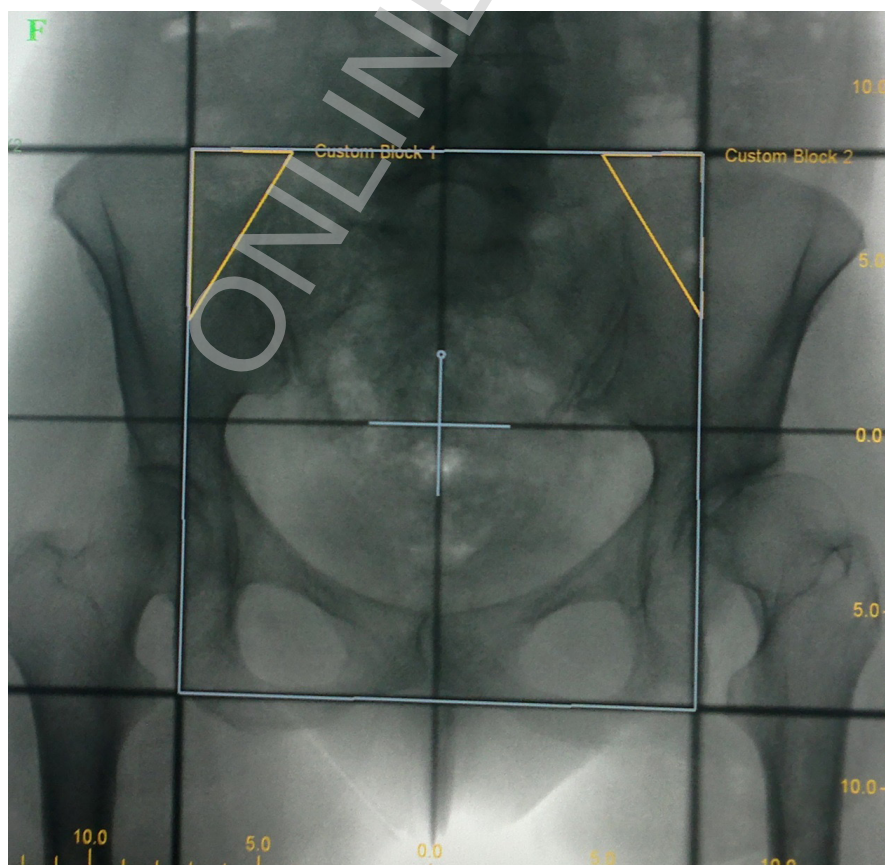


Figure 1. Conventional two-dimensional external beam radiotherapy (2D-EBRT) technique for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

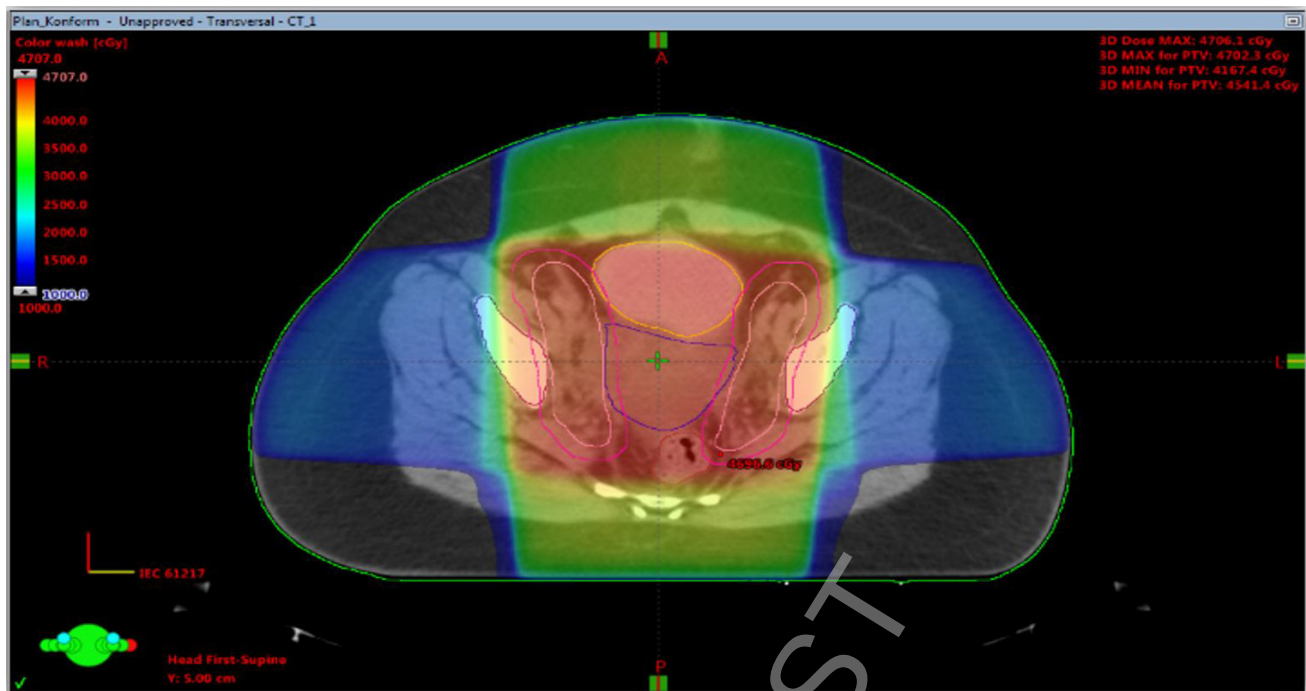


Figure 2. Axial CT image illustrating three-dimensional conformal radiotherapy (3D-CRT) planning using the four-field box technique for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

at risk achieved with contemporary external beam radiotherapy techniques, which have been associated with lower rates and severity of treatment-related toxicity (7). Figures 4 and 5 illustrate conventional X-ray-based two-dimensional intracavitary brachytherapy planning using orthogonal anteroposterior and lateral radiographs. This approach relied on predefined anatomical reference points and did not allow accurate assessment of target

volume coverage or dose to organs at risk. Finally, Figures 6 and 7 demonstrate modern three-dimensional image-guided brachytherapy, including MRI-guided treatment planning and three-dimensional reconstruction of combined intracavitary/interstitial brachytherapy, enabling highly individualized dose optimization according to tumor size, shape, and extent while improving sparing of surrounding organs at risk.

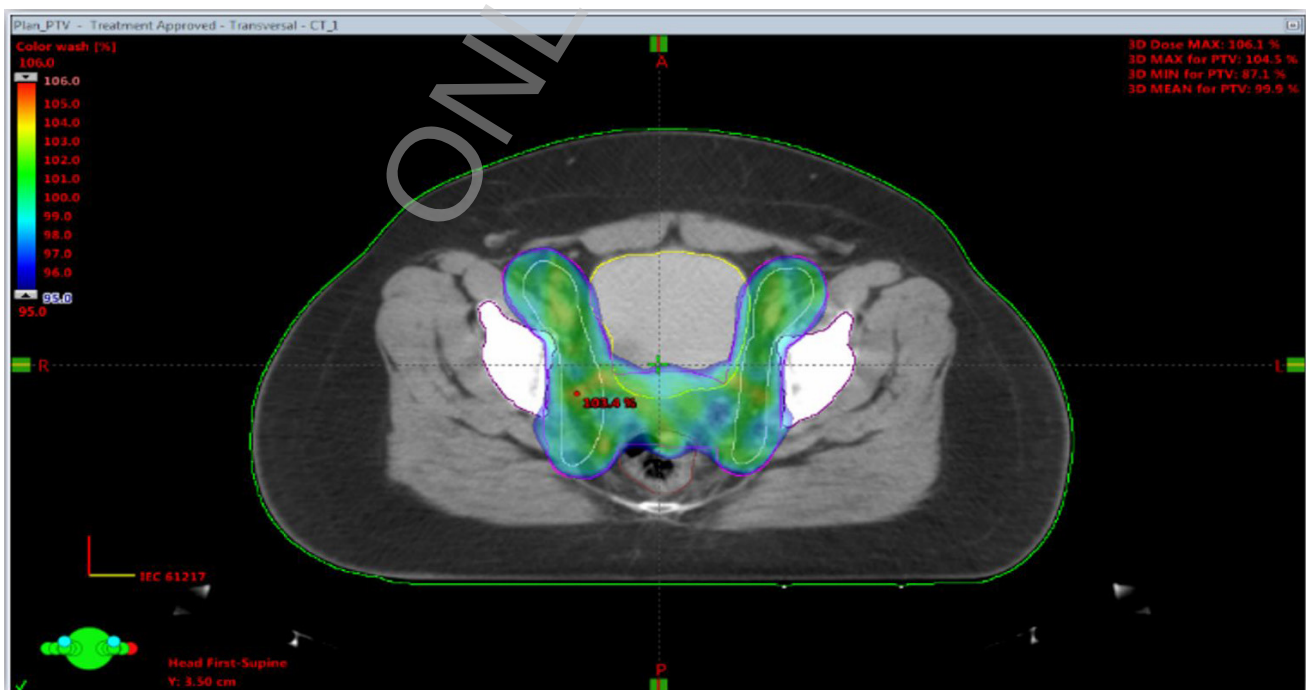


Figure 3. Axial CT image illustrating volumetric modulated arc therapy (VMAT) treatment planning with improved dose conformity and sparing of organs at risk (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

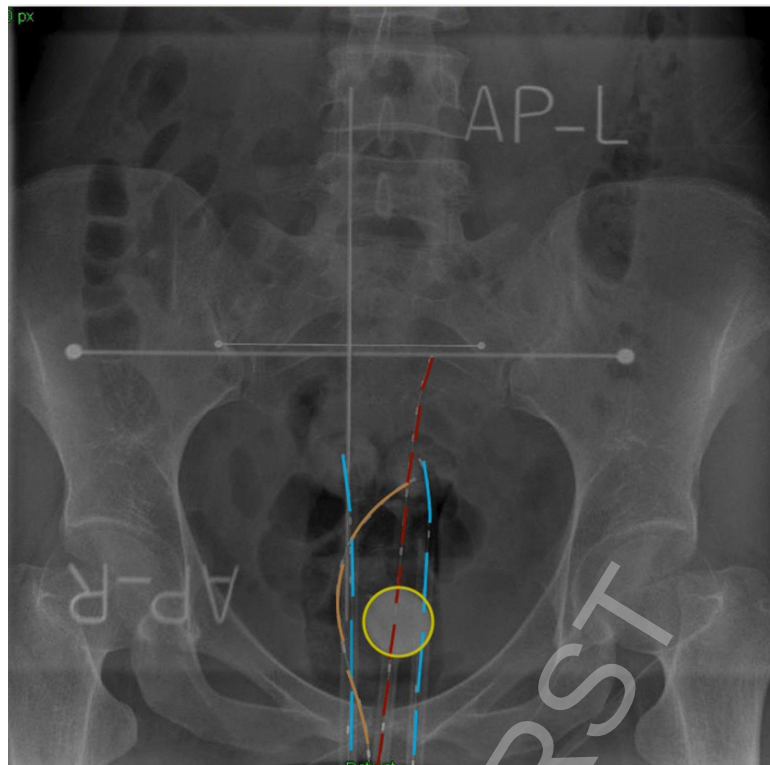


Figure 4. Anteroposterior radiograph illustrating conventional two-dimensional intracavitary brachytherapy planning for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

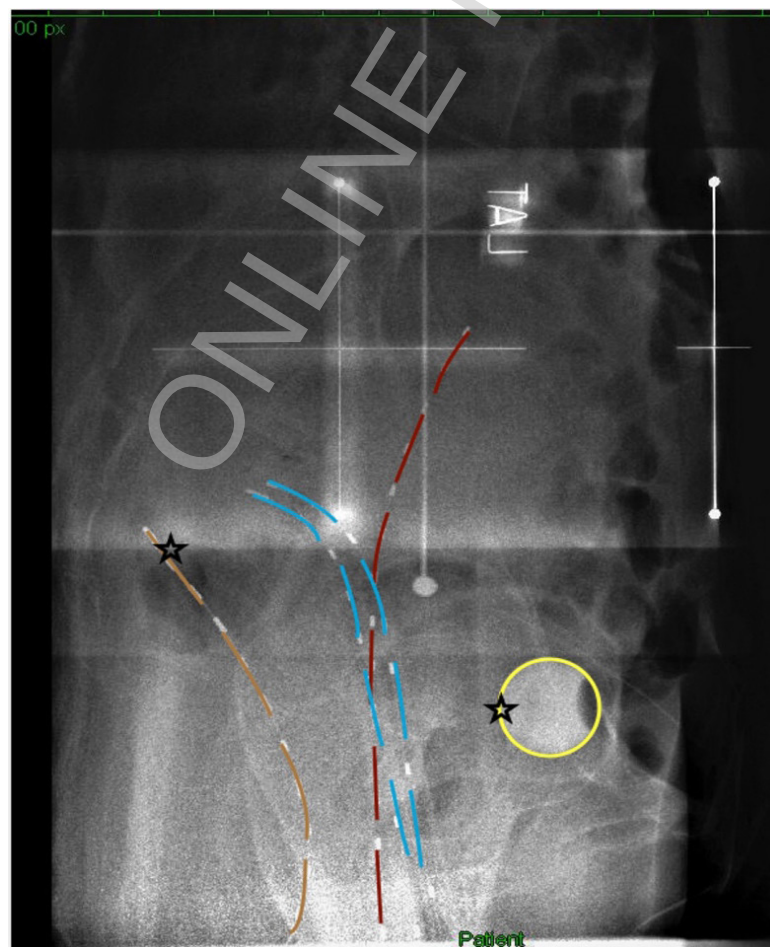


Figure 5. Lateral radiograph illustrating conventional two-dimensional intracavitary brachytherapy planning for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

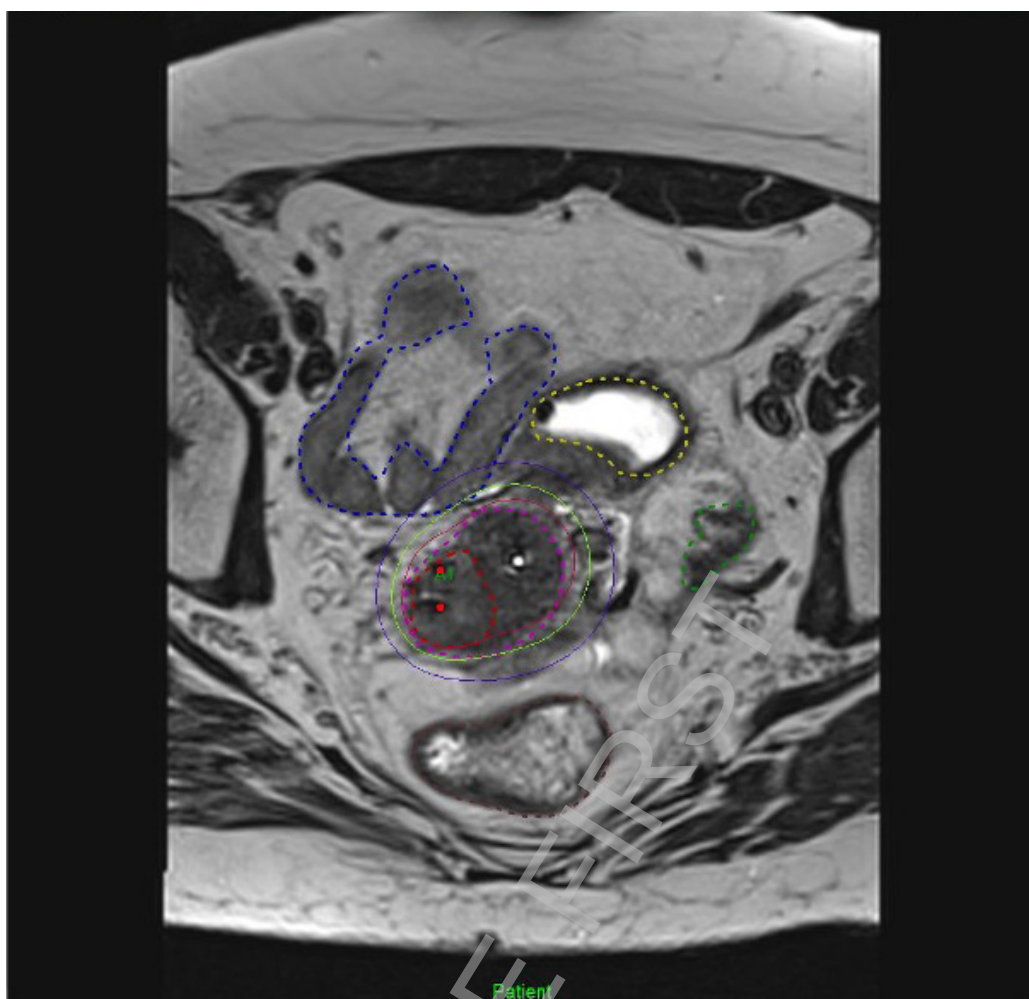


Figure 6. Magnetic resonance image demonstrating target volume delineation and dose distribution during MRI-guided adaptive brachytherapy (IGABT) for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

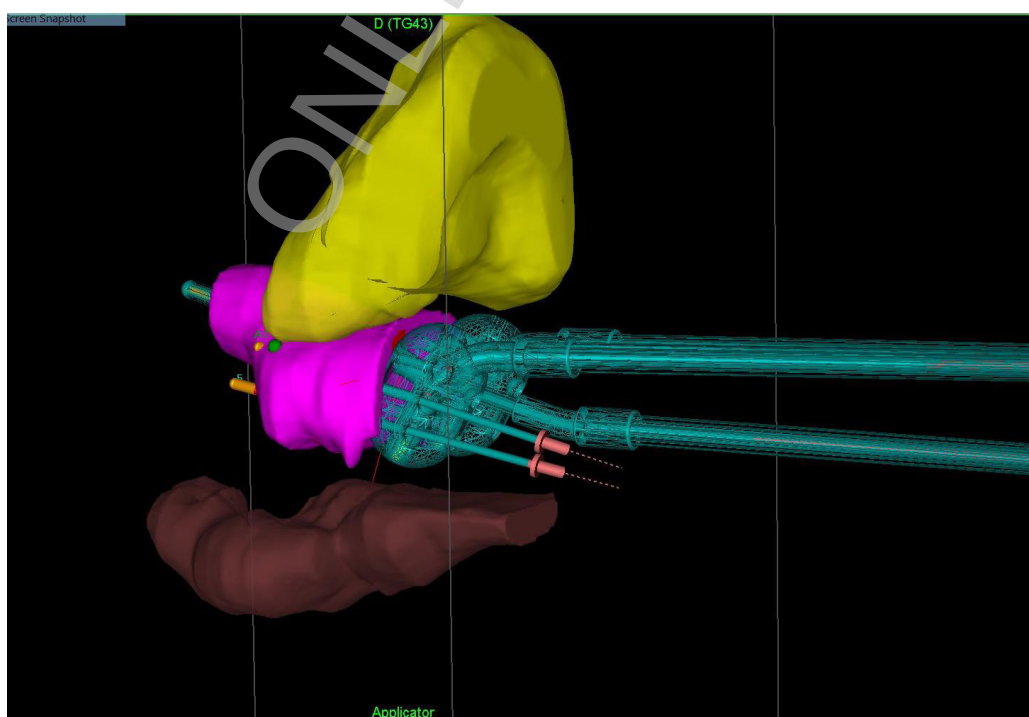


Figure 7. Three-dimensional reconstruction illustrating MRI-guided combined intracavitary/interstitial brachytherapy planning for locally advanced cervical cancer (Source: Institutional archive, Department of Radiation Oncology, Institute for Oncology and Radiology of Serbia).

Changes in chemotherapy administration, particularly regarding the number of delivered cisplatin cycles, should also be interpreted in the context of the widespread adoption of concurrent weekly cisplatin with radiotherapy as the standard treatment for locally advanced cervical cancer following the publication of pivotal clinical trials (6,13). Together, these developments reflect the evolution of definitive chemoradiotherapy toward more standardized and technologically advanced treatment approaches.

Despite these advances, the implementation of modern treatment strategies may vary across institutions and time periods depending on available resources, infrastructure, and clinical protocols. Evaluating temporal changes in treatment delivery within a single institution may therefore provide valuable insight into the evolution of clinical practice in the management of locally advanced cervical cancer.

MATERIALS AND METHODS

Study design and patients

This retrospective single-center cohort study was conducted at the Institute for Oncology and Radiology of Serbia, a tertiary referral center for gynecologic oncology. The study included 200 patients with locally advanced cervical cancer treated with definitive chemoradiotherapy.

Two cohorts were analyzed based on the treatment period: 100 consecutively selected patients from 2010–2011 and 100 consecutively selected patients from 2022–2023. These time periods were selected to reflect two distinct phases in the implementation of modern radiotherapy techniques at our institution. All included patients were consecutively selected to minimize selection bias.

Eligible patients were women with histologically confirmed cervical cancer and locally advanced stage of the disease (FIGO IIB–IVA), treated with definitive chemoradiotherapy. Patients treated surgically or with palliative intent, those with previous pelvic irradiation, and those with incomplete treatment records were excluded. No upper age limit was applied, and patients were included regardless of comorbidity status.

Clinical and treatment data were retrospectively collected from institutional medical records. Disease staging was determined based on clinical examination and imaging findings (CT and/or MRI). For this study, patients treated in 2010–2011 were retrospectively restaged according to the FIGO 2018 classification (4) using the available clinical and imaging data, to ensure comparability between the two study cohorts.

Treatment characteristics

All patients were treated with definitive concurrent chemoradiotherapy according to institutional protocols

in place at the time of treatment, aligned with contemporary clinical guidelines (6,12). All patients had initially been considered candidates for definitive chemoradiotherapy following multidisciplinary tumor board evaluation. Although ECOG performance status was not retrospectively analyzed, patients receiving radical treatment were generally required to have an adequate performance status compatible with definitive chemoradiotherapy. In some cases, concurrent chemotherapy was omitted after medical oncology assessment due to comorbidities, performance status, or other clinical considerations, and these patients received definitive radiotherapy alone.

In the earlier period (2010–2011), external beam radiotherapy (EBRT) was delivered using two-dimensional (2D) or three-dimensional conformal (3D-CRT) techniques. Treatment planning was based on conventional simulation and CT imaging, with standard fractionation schedules (1.8–2 Gy per fraction) to a total dose of 45–50 Gy. In patients with radiologically identified para-aortic lymphadenopathy, extended-field radiotherapy including the para-aortic region was performed. External beam radiotherapy was delivered using linear accelerators with photon energies of 6–15 MV.

In the later period (2022–2023), EBRT was delivered using modern techniques, including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), with image-guided radiotherapy (IGRT). Planning was performed using CT simulation for all patients, with MR co-registration applied in selected cases to improve tumor volume delineation. This approach enabled improved target delineation and dose conformity, as well as more precise sparing of organs at risk. In selected patients with radiologically involved lymph nodes, dose escalation using a simultaneous integrated boost (SIB) was performed in accordance with contemporary treatment protocols (6,12).

Following EBRT, all patients underwent intracavitary brachytherapy using high-dose-rate (HDR) remote afterloading technique with Iridium-192 sources. Standard applicators consisting of a uterine tandem and vaginal ovoids were used, with occasional use of a vaginal cylinder. In the earlier period, treatment planning was primarily based on orthogonal radiographs and the Manchester system, while in the later period, brachytherapy planning increasingly incorporated CT or, more often, MRI-guided brachytherapy (IGABT).

The prescribed brachytherapy dose to point A (or corresponding tumor volumes for IGABT planning) ranged from 28 to 35 Gy, delivered in 4–5 fractions. Concurrent chemotherapy was administered according to the treating medical oncologist's instructions. Among patients who received concurrent chemotherapy, cisplatin (CDDP) was administered at a dose of 40 mg/m² once weekly. Chemotherapy was administered approximately 4 hours before radiotherapy.

All treatment procedures were conducted in accordance with the clinical guidelines and recommendations valid at the time of treatment, reflecting contemporaneous National Comprehensive Cancer Network (NCCN) and GEC-ESTRO guidance and evolving standards of care, with treatment approaches adapted over time in line with advancements in international clinical practice (6,12).

Treatment-related variables analyzed in this study included:

- administration of concurrent chemotherapy (yes/no)
- number of chemotherapy cycles
- EBRT technique
- EBRT fractionation and total dose
- brachytherapy applicator type
- brachytherapy total dose
- number of brachytherapy applications

The described treatment-related parameters were subsequently compared between the two time periods to assess temporal changes in the delivery of definitive chemoradiotherapy.

Data collection

Clinical and treatment data were retrospectively collected from institutional medical records. All data were anonymized before analysis.

Statistical analysis

Continuous variables were presented as median values with range, while categorical variables were expressed as absolute numbers and percentages.

Comparisons between the two cohorts were performed using the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate based on expected frequencies.

All statistical tests were two-sided, and p -values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (IBM Corp., Armonk, NY, USA).

Ethical considerations

This retrospective study used data from existing medical records. The study protocol was reviewed and approved by the Ethics Committee of the Institute of Oncology and Radiology of Serbia (approval number: 0101/2026/1108). The Ethics Committee waived the requirement for written informed consent due to the study's retrospective nature. All data were anonymized, and patient confidentiality was maintained in accordance with applicable data protection regulations.

RESULTS

Baseline characteristics

Baseline patient and disease characteristics are presented in **Table 1**. Patients treated in 2022–2023 were significantly older than those treated in 2010–2011 (median age 56 vs. 51 years, $p = 0.005$). The proportion of patients with radiologically positive lymph nodes was significantly higher in the later cohort (63% vs. 41%, $p = 0.002$). Histological subtype distribution differed modestly between the study periods ($p = 0.046$), whereas no significant differences were observed in FIGO stage group distribution ($p = 0.143$) or the prevalence of comorbidities (54% vs. 42%, $p = 0.089$).

Chemotherapy

Significant differences were observed in the administration of concurrent chemotherapy between the two cohorts. All patients treated during 2010–2011 received concurrent chemotherapy, compared with 86% of patients treated during 2022–2023 ($p < 0.001$).

Among patients who received concurrent chemotherapy, the number of delivered cisplatin cycles differed significantly between the two treatment periods. Patients treated during 2010–2011 received more chemotherapy cycles than those treated during 2022–2023 ($p < 0.001$). The number of chemotherapy cycles was

Table 1. Baseline patient and disease characteristics according to treatment period

Characteristic	2010–2011 (n=100)	2022–2023 (n=100)	p-value
Age, median (range), years	51 (26–73)	56 (29–80)	0.005
FIGO stage II, n (%)	37 (37%)	38 (38%)	
FIGO stage III, n (%)	46 (46%)	54 (54%)	
FIGO stage IV, n (%)	17 (17%)	8 (8%)	0.143
Squamous cell carcinoma, n (%)	83 (83%)	92 (92%)	
Adenocarcinoma, n (%)	10 (10%)	8 (8%)	
Other histology, n (%)	7 (7%)	0 (0%)	0.046
Positive lymph nodes, n (%)	41 (41%)	63 (63%)	0.002
Presence of comorbidities	42 (42%)	54 (54%)	0.089

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Concurrent chemotherapy characteristics between the two treatment periods

Variable	2010–2011 (n=100)	2022–2023 (n=100)	p-value
Chemotherapy administered			<0.001
No	0 (0%)	14 (14%)	
Yes	100 (100%)	86 (86%)	
Number of cycles			<0.001
1–2	4 (4%)	15 (15%)	
3	5 (5%)	21 (21%)	
4	15 (15%)	34 (34%)	
5	76 (76%)	15 (15%)	
≥ 6	0 (0%)	1 (1%)	

Note: The number of chemotherapy cycles is presented only for patients who received concurrent chemotherapy (n = 100 in the 2010–2011 cohort and n = 86 in the 2022–2023 cohort); percentages are calculated relative to the entire cohort.

analyzed only among patients who received concurrent chemotherapy.

The characteristics of concurrent chemotherapy across the two treatment periods are summarized in [Table 2](#).

External beam radiotherapy

Substantial differences in the delivery of external beam radiotherapy (EBRT) were identified between the two cohorts. A complete shift in radiotherapy technique was observed between the two time periods, with modern radiotherapy techniques being exclusively used in the later cohort ($p < 0.001$).

Radiotherapy techniques were categorized as follows:

- Technique 1 – two-field technique (AP–PA): a conventional technique using two opposed anterior–posterior fields.
- Technique 2 – four-field box technique (4-field box): a conventional three-dimensional conformal radiotherapy (3D-CRT) technique using four fields (anterior, posterior, and two lateral fields).
- Technique 3 – intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT).

The number of EBRT fractions differed significantly between the two periods, indicating a change in fractionation patterns over time ($p < 0.001$). EBRT fractionation was categorized according to the total number of delivered fractions as follows: 25 (category 1), 24 (category 2), 23 (category 3), 27 (category 4), 22 (category 5), 19 (category 6), and 10 (category 7). For analytical purposes, less frequent regimens (27, 22, 19, and 10 fractions) were grouped into a single category.

Furthermore, the distribution of total EBRT dose differed significantly between the two treatment periods ($p < 0.001$), with dose escalation using a simultaneous integrated boost (SIB) observed exclusively in the later cohort. Dose escalation with SIB was delivered to pathologic lymph nodes, most commonly to 55 Gy in pelvic lymph nodes and up to 57.5 Gy in para-aortic

lymph nodes, reflecting individualized treatment planning.

Lower total EBRT doses were observed in a small number of patients in the earlier cohort (18 Gy in 10 fractions and 35.6 Gy in 19 fractions) and were primarily due to treatment interruptions caused by poor tolerance to radiotherapy. These rare dose values (18 Gy and 35.6 Gy) were grouped under the “Other” category to improve clarity in the tabular presentation.

In contrast, dose escalation to 50 Gy to the pelvic field in the earlier period was performed in selected patients when clinically indicated, reflecting an attempt to achieve improved local control within the limitations of conventional radiotherapy techniques.

External beam radiotherapy characteristics, including treatment technique, fractionation patterns, and total dose to the pelvic field (with or without SIB), are presented in [Table 3](#).

Brachytherapy

Further differences were observed in brachytherapy parameters between the two time periods.

Brachytherapy applicator types were categorized as follows: type 1 – uterine tandem with vaginal ovoids (standard intracavitary applicator), type 2 – uterine tandem with vaginal cylinder, and type 3 – combined use of a uterine tandem, vaginal cylinder, and ovoids. The distribution of applicator types did not differ significantly between the cohorts ($p = 0.374$).

Brachytherapy dose levels corresponded to the total prescribed dose and included 35, 33, 28, 14, 24, 7, 36, 34, and 42 Gy. The most frequently prescribed dose was 35 Gy, corresponding to standard treatment protocols.

For tabular presentation, dose levels were grouped into three categories: 35 Gy, 28 Gy, and other dose levels. The “other dose levels” category included less frequently used regimens (33, 14, 24, 7, 36, 34, and 42 Gy), which were combined due to their low frequency within the study population.

Table 3. External beam radiotherapy characteristics between the two treatment periods

Variable	2010–2011 (n=100)	2022–2023 (n=100)	p-value
Radiotherapy technique			<0.001
Technique 1	90 (90%)	0 (0%)	
Technique 2	10 (10%)	0 (0%)	
Technique 3	0 (0%)	100 (100%)	
Fractionation			<0.001
Category 1	47 (47%)	96 (96%)	
Category 2	35 (35%)	4 (4%)	
Category 3	13 (13%)	0 (0%)	
Other	5 (5%)	0 (0%)	
Total EBRT dose			<0.001
45 – 46 Gy pelvic field	97 (97%)	57 (57%)	
45 – 46 Gy pelvic field + SIB (pelvic ± para-aortic LN)	0 (0%)	43 (43%)	
50 Gy pelvic field	1 (1%)	0 (0%)	
Other	2 (2%)	0 (0%)	

Abbreviations: EBRT, external beam radiotherapy; SIB, simultaneous integrated boost; LN, lymph nodes.

Both 35 Gy (5×7 Gy) and 28 Gy (4×7 Gy) are standard brachytherapy schedules, with the former typically used in point A–based planning and the latter more commonly used in modern image-guided, volume-based approaches.

In the earlier treatment period, dose prescription was primarily based on point A. In contrast, in the later period, a transition toward 3D image-guided brachytherapy was observed, with dose increasingly defined using volumetric parameters. This reflects the evolution of brachytherapy planning toward more individualized and anatomically conformal treatment.

A statistically significant difference in dose distribution was observed between the two periods (chi-square test, $p = 0.001$). This was characterized by a lower proportion of patients receiving the 35 Gy regimen in the later period, along with increased use of the 28 Gy regimen

and other dose schedules, reflecting greater variability in prescribed doses ($p < 0.001$).

Brachytherapy application schedules were categorized according to the total number of delivered applications into three groups: Group 1 (5 applications), Group 2 (4 applications), and Group 3 (<4 applications). A statistically significant difference in application patterns was observed between the two treatment periods (Fisher's exact test, $p = 0.028$). Although five applications remained the most common schedule in both cohorts, the later period showed a shift toward a more heterogeneous distribution, including the introduction of four-application schedules and a higher proportion of patients treated with fewer than four applications.

Brachytherapy characteristics, including applicator type, total brachytherapy dose, and application patterns, are presented in **Table 4**.

Table 4. Brachytherapy characteristics between the two treatment periods

Variable	2010–2011 (n=100)	2022–2023 (n=100)	p-value
Applicator type			0.374
Type 1	75 (75%)	84 (84%)	
Type 2	11 (11%)	7 (7%)	
Type 3	14 (14%)	9 (9%)	
Total dose (Gy) - dose categories			<0.001
35 Gy	84 (84%)	67 (67%)	
28 Gy	9 (9%)	20 (20%)	
Other	7 (7%)	13 (13%)	
Number of applications			0.028
5	88 (88%)	78 (78%)	
4	0 (0%)	5 (5%)	
< 4	12 (12%)	17 (17%)	

DISCUSSION

This study demonstrates significant temporal changes in the delivery of definitive chemoradiotherapy for patients with locally advanced cervical cancer over a period of more than a decade. The findings indicate substantial modifications in chemotherapy administration, radiotherapy techniques, and brachytherapy parameters, reflecting the evolution of clinical practice and the implementation of modern treatment approaches. Baseline patient and disease characteristics differed to some extent between the two cohorts, particularly with regard to age, histological subtype distribution, and nodal status. These differences should be considered when interpreting the observed temporal changes in treatment delivery.

One of the most important findings of this study is the marked shift in external beam radiotherapy (EBRT) technique. A complete transition from older radiotherapy techniques to modern approaches was observed in the later cohort, which is consistent with the global adoption of IMRT, VMAT, and image-guided radiotherapy (7–9). These advancements have enabled greater dose conformity and organ-at-risk sparing, contributing to more precise and standardized treatment delivery.

Importantly, the introduction of modern IMRT/VMAT-based techniques has also enabled the delivery of a simultaneous integrated boost (SIB) to radiologically pathologic lymph nodes. Such an approach was not feasible with older radiotherapy techniques, which relied primarily on two- or three-dimensional conformal planning. In those settings, treatment was limited to field border adjustments to encompass nodal regions, without the option of selective dose escalation to involved lymph nodes while maintaining acceptable doses to surrounding normal tissues (14–18).

The ability to deliver SIB is particularly important in patients with node-positive disease, as dose escalation to involved lymph nodes has been associated with improved nodal control. Previous studies have shown that IMRT-based SIB to PET/CT-positive lymph nodes can achieve high local control rates with acceptable toxicity profiles in locally advanced cervical cancer (19–21). Therefore, the observed transition in radiotherapy technique represents not only a technological advancement but also an increased capacity for treatment individualization and dose intensification in high-risk regions.

An additional important aspect that should be considered when interpreting these findings is the evolution of diagnostic imaging over time. In the earlier treatment period, access to advanced imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET/CT) was more limited. Consequently, radiotherapy planning was largely based on less precise imaging and clinical assessment, which was consistent with the use of two-dimensional techniques.

In contrast, the later period was characterized by increased availability and routine use of modern imaging, enabling more detailed tumor delineation and the detection of nodal disease. This shift in diagnostic capabilities necessitated the implementation of more advanced radiotherapy techniques, such as IMRT and image-guided radiotherapy, to exploit the benefits of improved staging and target definition fully.

Therefore, the observed transition in radiotherapy delivery reflects not only technological advancements in treatment but also parallel progress in diagnostic imaging, both of which contribute to more precise and individualized management of locally advanced cervical cancer.

In addition to technological improvements, significant differences in EBRT fractionation and dose distribution were observed between the two cohorts. The latter treatment period demonstrated a more uniform fractionation pattern, suggesting increased standardization of treatment protocols over time.

These findings suggest a progressive evolution toward more advanced radiotherapy techniques, enabling more consistent treatment planning, with the majority of patients in the later period receiving conventional fractionation (45 Gy in 25 fractions, 1.8 Gy per fraction). This is likely attributable to the availability of modern treatment planning systems and greater adherence to contemporary clinical guidelines (6).

An additional factor that may explain the observed differences in brachytherapy dose and the number of applications between the two periods is the limitations of earlier radiotherapy techniques. In the 3D-CRT era, dose escalation to the tumor was more challenging due to the limited conformality of external beam radiotherapy, which was commonly complemented by more uniform brachytherapy schedules, predominantly consisting of five applications. This is reflected in our cohort, where the majority of patients in the earlier period received 5 applications (88%), with no patients receiving 4 applications and only a small proportion receiving fewer than 4 (12%). This approach reflects the limited precision of target delineation and dose delivery in the pre-image-guided era.

In contrast, the introduction of modern techniques such as IMRT/VMAT and image-guided radiotherapy, together with CT/MRI-based image-guided adaptive brachytherapy (IGABT), has enabled more accurate target delineation and improved sparing of organs at risk. These advances allow for higher dose conformity and more efficient fractionation schedules, supporting the use of four BRT applications, which are now widely adopted in contemporary clinical practice. In our later cohort, this shift is evident, with a decrease in the proportion of patients treated with five applications (78%) and the introduction of four-application schedules (5%). This shift is consistent with GEC-ESTRO-based concepts of image-guided brachytherapy and dose optimization strategies, as well as international consensus recommendations

(10,13,22). Consequently, the later period shows a broader distribution of fractionation patterns. In contrast, cases with fewer than 4 applications are more likely to reflect clinical limitations or patient-related factors rather than planned treatment strategies.

Changes in chemotherapy administration were also observed. Although concurrent chemotherapy remained a key component of treatment, differences in its use and the number of cycles delivered were evident between the two periods. Patients in the earlier cohort generally received more concurrent chemotherapy cycles than those in the more recent cohort. Several factors may have influenced these differences. Patients treated in 2022–2023 were older than those treated in 2010–2011, and a higher proportion had documented comorbidities. In addition, current clinical practice emphasizes careful assessment before each chemotherapy cycle, particularly about hematologic toxicity, the most common dose-limiting adverse effect of concurrent chemoradiotherapy. This approach aims to minimize treatment-related toxicity while avoiding interruptions or compromise of radiotherapy, which is the key component of definitive treatment. Advances in diagnostic assessment may also have enabled more accurate risk stratification, supporting a more individualized treatment approach rather than uniform treatment for all patients (6,13).

Regarding brachytherapy, significant differences were observed in both the total dose and the number of applications, while the type of applicator remained comparable across groups. These findings are consistent with the gradual transition toward more individualized and image-guided brachytherapy approaches, which facilitate dose optimization while maintaining established organ-at-risk constraints (10,11).

Cases with fewer than four brachytherapy applications were not part of the planned definitive treatment schedule. In clinical practice, such treatment is most commonly delivered with palliative (hemostatic) intent, whereas incomplete brachytherapy may less frequently result from poor treatment tolerance or significant comorbidities. Because the study was retrospective, the specific indication for fewer than 4 brachytherapy applications could not be reliably determined.

The observed transition reflects the gradual institutional adoption of modern radiotherapy technologies and their integration into routine clinical practice. The implementation process included additional training for radiation oncologists, medical physicists, and radiation therapists to support the introduction of new treatment planning and delivery systems. At present, older radiotherapy techniques are predominantly used for selected palliative indications, while modern techniques are the standard approach for definitive treatment.

Overall, the results of this study reflect real-world clinical practice within a single tertiary institution and provide insight into how technological developments and

evolving treatment strategies have influenced treatment delivery over time.

This study has several limitations. Its retrospective design introduces the possibility of selection bias and incomplete data collection. Although conducted at a single center, the study was conducted at a high-volume tertiary referral institution, which may strengthen the external validity of the findings, particularly in comparable healthcare settings; however, caution is warranted when extrapolating the results to environments with substantially different resources and patient populations. Additionally, clinical outcomes such as treatment response, survival, and toxicity were not evaluated, limiting the ability to assess the direct clinical impact of the observed changes in treatment delivery. While these findings provide valuable insight into evolving treatment practices, further studies incorporating outcome data are needed to determine their clinical significance. The primary aim of this study was to assess temporal changes in treatment delivery rather than clinical outcomes; therefore, future studies integrating survival and toxicity data are warranted to evaluate the clinical impact of these findings better.

CONCLUSION

This study demonstrates the evolution of definitive chemoradiotherapy for locally advanced cervical cancer over the past decade. The observed changes reflect the implementation of contemporary radiotherapy techniques and advances in brachytherapy planning and delivery.

The transition to advanced radiotherapy approaches has enabled dose intensification in selected high-risk regions, including pathologic lymph nodes. In parallel, the increased availability of modern imaging modalities has supported more accurate staging and target delineation, facilitating the adoption of contemporary treatment approaches. Importantly, these findings demonstrate that the transition from conventional to modern radiotherapy techniques can be successfully implemented in a real-world setting within a middle-income country.

They also provide insight into the evolution of clinical practice in the management of locally advanced cervical cancer. They may serve as a useful reference for other middle-income countries undergoing similar modernization of radiotherapy services.

Acknowledgments: N/A

Funding information: The authors declare that this study received no external funding.

Conflicts of interest: The authors declare no conflict of interest.

Author contributions: Conceptualization: J.S. and M.P.V.; Methodology: J.S. and M.P.V.; Data collection: J.S., I.S., L.J., and M.J.; Statistical analysis: D.G.; Data analysis: J.S.; Investigation: P.N., M.R., M.V., and M.J.; Writing – original draft: J.S.; Writing – review and

editing: M.P.V., I.S., L.J., P.N., M.R., M.V., M.J., D.G., and A.T.; Supervision: M.P.V. and A.T. All authors have read and approved the final manuscript.

Ethical approval: This retrospective study was conducted using data obtained from existing medical records. The study protocol was reviewed and approved by the

Ethics Committee of the Institute of Oncology and Radiology of Serbia (approval number: 0101/2026/1108). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent: The Ethics Committee waived consent due to the study's retrospective nature.

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VREMENSKE PROMENE U PRIMENI DEFINITIVNE HEMIORADIOTERAPIJE KOD LOKALNO UZNAPREDOVALOG KARCINOMA GRLIĆA MATERICE: RETROSPEKTIVNA JEDNOCENTRIČNA STUDIJA

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Sažetak

Uvod: Pacijentkinje sa lokalno uznapredovalim karcinomom grlića materice (LACC) standardno se leče definitivnom hemioradioterapijom (CRT), koja obuhvata spoljašnje zračenje (EBRT), konkomitantnu hemioterapiju i brahiterapiju. Tokom protekle decenije, napredak u radioterapijskim tehnikama i imidžingu doveo je do značajnih promena u sprovođenju terapije. Cilj ove studije bio je da se procene vremenske promene u primeni CRT.

Metode: Retrospektivna jednocentrična kohortna studija obuhvatila je 200 pacijentkinja sa LACC lečenih definitivnom CRT u Institutu za onkologiju i radiologiju Srbije. Analizirane su dve kohorte: 100 pacijentkinja lečenih u periodu 2010–2011. godine i 100 pacijentkinja lečenih u periodu 2022–2023. godine. Upoređivane su bazalne karakteristike pacijentkinja i parametri lečenja, uključujući primenu hemioterapije, tehniku spoljašnjeg zračenja, dozu i frakcionisanje, kao i karakteristike brahiterapije.

Rezultati: Uočene su značajne razlike između dve ko-

horte. Primena konkomitantne hemioterapije i broj primenjenih ciklusa značajno su se razlikovali između posmatranih perioda ($p < 0,001$). U kasnijem periodu zabeležen je potpuni prelazak sa konvencionalnih radioterapijskih tehnika na IMRT/VMAT ($p < 0,001$), uz uvođenje simultanog integrisanog pojačanja doze (SIB). Takođe su uočene značajne razlike u frakcionisanju i ukupnoj dozi EBRT ($p < 0,001$). U brahiterapiji su registrovane značajne razlike u dozi i frakcionisanju ($p < 0,001$ i $p < 0,05$), dok je tip aplikatora ostao uporediv između grupa.

Zaključak: Uočene su značajne vremenske promene u primeni CRT, koje odražavaju primenu savremenih radioterapijskih tehnika i evoluciju terapijskih strategija. Rezultati ukazuju na veću individualizaciju lečenja i širu primenu savremenih radioterapijskih pristupa u rutinskoj kliničkoj praksi zdravstvenog sistema srednjeg nivoa razvijenosti.

Ključne reči: karcinom grlića materice, hemioradioterapija, IMRT, brahiterapija, radioterapijske tehnike

Primljen: 02.05.2026. | **Revidiran:** 03.07.2026. | **Prihvaćen:** 09.07.2026. | **Online First:** 16.07.2026.

Medicinska istraživanja 2026