

**UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE**



**VAGINAL MORBIDITY AND SEXUAL QUALITY OF LIFE IN
WOMEN TREATED FOR LOCALLY ADVANCED CERVICAL
CANCER USING 3D IMAGE-GUIDED INTRACAVITARY-
INTERSTITIAL BRACHYTHERAPY**

PHD THESIS SUMMARY

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Introduction

The standard treatment for locally advanced cervical cancer involves a multimodal approach based on concurrent chemoradiotherapy followed by image-guided adaptive brachytherapy (IGABT), the latter leading to a significant improvement in local control and survival by enabling the administration of high tumoricidal doses while protecting organs at risk. However, the occurrence of late functional effects, especially at the vaginal level, affects patients' sexual function, body image, and quality of life. The general objective of the research was to evaluate the oncological and functional outcomes, vaginal morbidity, and the impact on sexual function and quality of life in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy followed by IGABT. To this end, therapeutic outcomes, the incidence and severity of late toxicities, dose-effect correlations, and the impact of treatment on functional recovery and quality of life were analysed using internationally validated tools.

Specific objectives of the study are:

- Analysis of oncological outcomes and therapeutic parameters in a representative cohort;
- Quantifying the impact of treatment on sexual function and quality of life using internationally validated tools;
- Identifying predictive clinical factors and dose-effect correlations that influence the occurrence of pelvic adverse effects;
- Formulating multidisciplinary practical recommendations for optimizing brachytherapy (BT) plans and implementing functional rehabilitation strategies.

The thesis is structured into two main parts. The first part synthesizes current data from the specialized literature regarding the epidemiology of cervical cancer, the principles of adaptive radiotherapy, and the mechanisms of post-irradiation vaginal morbidity [1–3]. The second part includes personal contributions and the results of clinical studies conducted on a cohort of patients treated in an oncology centre in Romania, highlighting both the oncological efficacy of CT-guided IGABT and its impact on quality of life and sexual function. Through the obtained results, this thesis contributes to the development of a modern perspective on therapeutic success in cervical cancer, demonstrating that the evaluation of treatment efficacy must include not only disease control and survival but also the functional and psychosocial dimensions of patient recovery.

I. GENERAL PART

1. Locally advanced cervical cancer and multimodal radiotherapeutic management

1.1 Epidemiology, etiopathogenesis, and global and national risk factors

Cervical cancer is one of the most frequent causes of oncological morbidity and mortality in women [4]. Persistent infection with oncogenic HPV represents the main etiological factor [5,6], while disease progression is favoured by factors such as smoking, immunosuppression, multiparity, and low socioeconomic status [7–9]. Although vaccination and screening programs have reduced the incidence in many developed regions, numerous patients are still diagnosed at locally advanced stages, requiring complex multimodal treatments associated with significant late effects on sexual function and quality of life.

1.2 Histopathological classification and staging (FIGO)

Histopathological classification has significant prognostic and therapeutic importance, influencing treatment response and disease progression. According to the WHO classification, the main histopathological types of cervical cancer are [10,11]: **1.** Squamous cell carcinoma (including the following subtypes: keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma); **2.** Adenocarcinoma (usual endocervical adenocarcinoma, mucinous adenocarcinoma, gastric-type adenocarcinoma); **3.** Adenosquamous carcinoma; **4.** Rare histological types.

Cervical cancer staging is performed according to the FIGO system, which represents the current standard used in clinical practice and research, revised in 2018.

1.3 External beam radiotherapy – principles and modern techniques

The standard curative treatment for locally advanced cervical cancer (FIGO IIB–IVA) is multimodal and consists of concurrent chemoradiotherapy (pelvic external beam radiotherapy combined with cisplatin) obligatorily followed by brachytherapy, which allows escalation of the tumour dose while sparing the organs at risk [12].

1.3.1 External Beam Radiotherapy – Principles and Modern Techniques

External beam radiotherapy represents the first stage of curative treatment in locally advanced cervical cancer, with the role of controlling the primary tumour and regional lymph nodes, reducing tumour volume, and rapidly alleviating symptoms (haemostasis and pain control), thus preparing the patient for brachytherapy [1,2]. The transition to modern IMRT/VMAT techniques, supported by MRI and PET-CT imaging, has enabled superior dose conformity, a significant reduction in gastrointestinal and genitourinary toxicity, and maintenance of oncologic efficacy, using a standard regimen of 45–50.4 Gy combined with cisplatin-based chemotherapy, with treatment completion within a maximum of 56 days to optimize survival [13].

1.3.2 Concurrent Chemoradiotherapy – Therapeutic Role and Toxicity

Concurrent chemoradiotherapy (RT combined with weekly cisplatin) represents the standard curative treatment for locally advanced cervical cancer, providing a significant survival and local control advantage compared with radiotherapy alone, while requiring careful monitoring of hematologic, renal, and neurologic toxicities in order to avoid treatment interruptions.

New therapeutic strategies are exploring optimization of treatment sequencing through induction chemotherapy and immunotherapy (with benefits demonstrated in studies such as INTERLACE and KEYNOTE-A18), whereas adjuvant chemotherapy after chemoradiotherapy has not demonstrated survival benefits and is associated with increased toxicity; therefore, it is not routinely recommended [14,15].

1.4 Brachytherapy in Cervical Cancer – Evolution and Therapeutic Role

Brachytherapy is a mandatory component of curative treatment in locally advanced cervical cancer according to the ESGO–ESTRO–ESP guidelines and cannot be replaced by increasing the EBRT dose, due to its superior dose conformity to the HR-CTV and better sparing of organs at risk [16].

Data from the EMBRACE-I study confirm the superiority of IGABT, demonstrating approximately 92% local control at 5 years and a significant reduction in severe toxicities compared with conventional techniques, establishing it as the gold standard. In contrast, SBRT remains only a salvage alternative in selected cases and cannot replace brachytherapy due to its dosimetric conformity limitations [1].

2. Image-Guided 3D Intracavitary–Interstitial Brachytherapy

2.1 Physical and Radiobiological Principles of IGABT

The physical principles of IGABT are based on the steep dose gradient and the inverse square law, which allow the delivery of very high doses to the tumour while sparing the adjacent healthy tissues. HDR brachytherapy uses Iridium-192 sources and “stepping source” technology, enabling three-dimensional optimization of dose distribution according to tumour extension [17].

2.2 Evolution of Application Techniques: The Transition from 2D to 3D and the Superiority of the Hybrid Technique (Intracavitary versus Intracavitary–Interstitial)

In the era of 2D techniques, brachytherapy was based on radiographs and dose prescription to “Point A,” without direct tumour visualization, which frequently resulted in underdosing of bulky lesions or overdosing of healthy tissues, leading to significant toxicity. The transition to IGABT enabled true treatment individualization through three-dimensional dose modelling according to residual anatomy and tumour extension, increasing HR-CTV coverage while simultaneously reducing the dose delivered to organs at risk and long-term vaginal morbidity [1].

2.3 3D Planning: Delineation of Target Volumes and Organs at Risk

3D planning in IGABT represents the foundation of modern adaptive brachytherapy, allowing treatment individualization according to the patient’s anatomy and tumour regression after chemoradiotherapy. The current approach uses adaptive target volumes redefined at each application to optimize dose distribution and protect organs at risk. MRI remains the gold standard for delineation of residual tumour due to its superior soft tissue contrast; however, CT represents an alternative in centres with limited access to MRI.

2.4 Therapeutic Balance: Tumour Control and Major Oncologic Outcomes

IGABT represents the modern standard that optimizes the therapeutic ratio through dose escalation to the HR-CTV ($\approx 85\text{--}90$ Gy EQD₂) while sparing organs at risk. According to the EMBRACE-I study, it achieves approximately 92% local control at 5 years and an overall survival rate of approximately 74%, with reduced severe toxicity. The hybrid intracavitary–interstitial technique is essential for advanced tumours, allowing dose conformity in parametrial extensions without increasing vaginal morbidity. Furthermore, the oncologic success of IGABT has shifted the focus of research toward late functional effects and patients’ quality of life [18,19].

3. Impact of Treatment on Pelvic Organs: Vaginal Morbidity, Sexual Function, and Quality of Life

3.1 Anatomy and Radiosensitivity of the Vagina. Types of Vaginal Toxicity

Radiation-induced vaginal morbidity results from the interaction between the complex structure of the vagina and ionizing radiation, leading to both acute inflammatory reactions (mucositis, ulcerations, adhesions) and late effects (stenosis, shortening, atrophy, dryness, and, rarely, fistulas).

3.2 Fibrosis, Stenosis, and Vaginal Dryness

The most frequent and disabling sequelae affecting the vaginal mucosa after brachytherapy for cervical cancer are vaginal stenosis, fibrosis, and vaginal dryness [20,21].

3.3 The PIBS System, Dose–Effect Relationship in Brachytherapy, and Vaginal Dosimetric Particularities

The PIBS system is based on a fixed bony landmark that is easily identifiable on sectional imaging. This point is used as an anatomical “zero” reference to define the longitudinal axis of the vagina, regardless of applicator position or anatomical distortions caused by the tumour [22,23].

3.4 Radiation-Induced Sexual Dysfunction and the Definition of Quality of Life (HRQoL) in Gynecologic Oncology

Post-treatment sexual dysfunction in cervical cancer is determined by a multifactorial mechanism involving the combined local effects of radiotherapy (stenosis, fibrosis, atrophy, dryness), treatment-induced ovarian insufficiency with decreased libido, and psychological factors (altered body image, anxiety, and relationship difficulties) [24].

3.5 Validated Assessment Instruments and the Importance of a Multidisciplinary Approach in Functional Survivorship

3.5.1 QoL and Sexual Function Assessment Instruments

Among the validated and widely used instruments for assessing quality of life and symptomatology are the general oncologic questionnaire EORTC QLQ-C30 and the cervical cancer-specific module EORTC QLQ-CX24. The latter evaluates treatment-specific toxicity, including vaginal symptoms and the impact on sexual function and sexual activity [25,26].

3.5.2 Importance of the Multidisciplinary Approach

Functional survivorship is not a secondary objective, but rather an integral component of modern post-therapeutic oncologic follow-up.

II. PERSONAL CONTRIBUTIONS

4. Research Hypothesis and General Objectives

The present work was based on the research hypothesis that CT- and ultrasound-guided IGABT provides effective oncologic local control, which can be assessed, but may also cause undesirable effects on physical, psychological, social, and/or sexual functioning, permanently altering the integrity of patients' intimate life through the development of vaginal morbidity and sexual dysfunction, the degree of impairment depending on the clinical characteristics and dosimetric parameters of treatment. In this context, the evaluation of clinical and functional outcomes provides relevant data both for regional practice and for the international literature.

The general objective of the research is the analysis of the outcomes of CT-guided IGABT in a population treated in an oncology centre in Romania, as well as the evaluation of clinical and functional results, vaginal morbidity, and the impact on sexual function and quality of life in patients with locally advanced cervical cancer.

This general objective was achieved in the present study through the following specific objectives:

- Analysis of oncologic outcomes (local control, survival) and therapeutic parameters (EBRT, waiting time, target volumes, etc.) in a representative cohort;
- Evaluation of the incidence, severity, and temporal dynamics of late vaginal toxicity;
- Quantification of the impact of treatment on sexual function and quality of life using internationally validated instruments;
- Predictive identification of clinical factors and dose–effect correlations influencing the occurrence of pelvic adverse effects;
- Formulation of practical multidisciplinary recommendations for optimization of BT plans and implementation of functional rehabilitation strategies.

To achieve these objectives, a detailed study was conducted to evaluate tumour control, survival, and acute toxicity in a cohort of patients diagnosed with locally advanced cervical cancer

and treated with concurrent chemoradiotherapy followed by image-guided adaptive brachytherapy (IGABT).

5. General Research Methodology

5.1 Research Plan and Patient Selection

The study included a cohort of 180 patients with locally advanced cervical cancer (FIGO IB3–IVA) treated with curative intent using EBRT and BT, from whom clinical, demographic, oncologic, and treatment-related data were collected from medical records, together with survival information. The cohort was evaluated using internationally validated questionnaires (EORTC QLQ-CX24 and QLQ-C30), employed for the analysis of health-related quality of life.

5.2 Clinical and Demographic Profile of the Study Cohort

5.2.1 Age and Presence of Comorbidities

The patients' ages ranged between 14 and 89 years, with a mean age at diagnosis of 54 years; 84.4% of the total cohort belonged to the 25–69 years age group, which is considered at risk for cervical cancer. An important clinical aspect influencing therapeutic decisions and treatment compliance is the presence of comorbidities. Figure 5.1 presents the distribution of comorbidities at diagnosis. A total of 65% of patients presented with at least one associated condition. It should also be noted that 35% of patients had no identified comorbidities. These comorbidities are highly important from the perspective of treatment and patient survival.

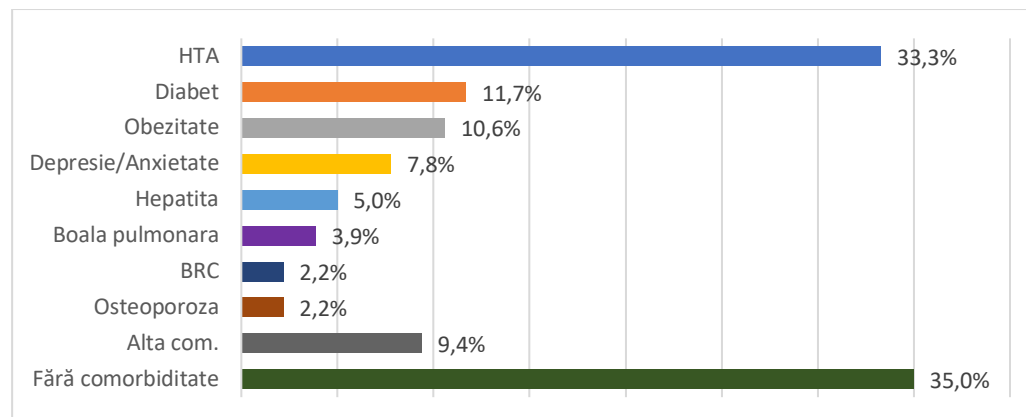


Figure 5.1 Main Comorbidities at Diagnosis

5.2.2 Tumour Characteristics and Imaging Evaluation

Figure 5.2 presents the distribution of women according to tumour dimensions; only 12.2% had tumours smaller than 30 cm³. One quarter of the cohort was diagnosed with tumours exceeding 100 cm³, highlighting the locally advanced nature of the disease at presentation and the need for complex, often interstitial, brachytherapy to achieve adequate dosimetric coverage.

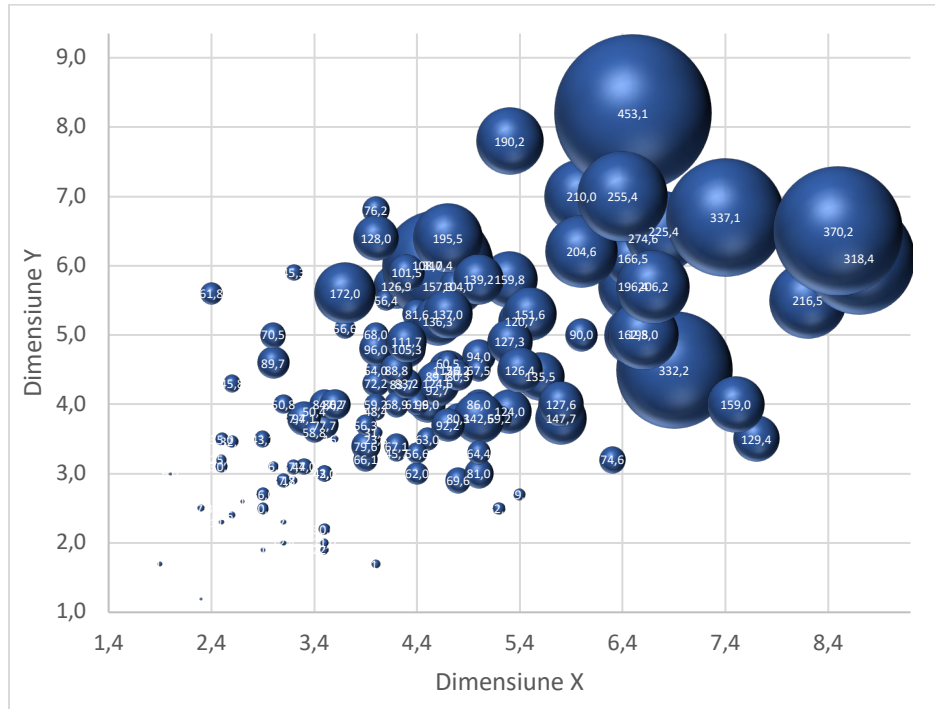


Figure 5.2 Distribution of Women According to X and Y Dimensions and Tumor Volume

5.2.3 Therapeutic Management and the Time Factor

Only 48.3% of patients started radiotherapy within the first 6 weeks after histopathological confirmation, while 26.6% initiated treatment within the first month following diagnosis. The mean waiting time until the start of radiotherapy was approximately 2 months.

5.3 Statistical Analysis

Statistical analyses were performed with the methodological support of a biostatistics specialist (see the Acknowledgements section). To quantitatively characterize the sample, a descriptive analysis was conducted (mean, median, standard deviation). Variability across different characteristics was analysed using indicators such as standard deviation, variance, or coefficient of homogeneity. To test associations and differences between subgroups, specific

statistical tests were applied, including the Student's t-test, Chi-square test (χ^2), Z-test, Kaplan–Meier curves, Log-rank (Mantel–Cox) test, ROC (Receiver Operating Characteristic) curves, and the Cox proportional hazards regression model. Multivariable Cox regression models for OS (overall survival) and LC (local control) included a priori established covariates: FIGO stage, HR-CTV D90 EQD₂, radiologic nodal status, and tumour size.

6. Clinical, Dosimetric, and Toxicity Outcomes of CT-Guided Hybrid Tandem-and-Ring Brachytherapy in Locally Advanced Cervical Cancer

6.1 Introduction

This chapter presents the clinical and dosimetric outcomes, as well as the toxicity profile associated with the use of CT-guided hybrid tandem-and-ring brachytherapy in the treatment of locally advanced cervical cancer. The analysis of these parameters is essential for evaluating the therapeutic efficacy and safety of image-guided 3D intracavitary–interstitial brachytherapy, which is increasingly used in modern oncologic practice. The dosimetric parameters and clinical outcomes obtained allow the correlation of tissue exposure with the occurrence of vaginal complications and with patient-reported changes in sexual function and quality of life.

The specific objective of this study is to evaluate the clinical outcomes, dosimetric parameters, and toxicity profile in patients with locally advanced cervical cancer treated with CT-guided IGABT (tandem and ring), with emphasis on the impact of treatment on vaginal morbidity and sexual quality of life.

6.2 Patients and methods

6.2.1 Characteristics of the Study Group and Initial Evaluation

This chapter represents a retrospective study conducted on a cohort of 180 patients with histologically confirmed LACC, stage IB1–IVA according to the FIGO 2018 staging system, treated at the SANADOR Oncology Centre between 2020 and 2022.

Clinical characteristics of the patients included: mean age 54 years, 38% perimenopausal, MRI and CT evaluation performed, and 82.8% presenting with lymph node involvement.

Histopathological and molecular profile: 67.8% were classified as FIGO stage IIIC1–IIIC2, 88.3% had SCC histology, 7.2% had adenocarcinoma (ADK), and tumour size was ≥ 50 mm in 56.7% of cases.

6.2.2 Therapeutic Protocol and Planning of CT-Guided Hybrid Brachytherapy

EBRT was primarily delivered using VMAT with 6 MV photons, with 75% of patients requiring extended-field para-aortic irradiation. All patients received EBRT at a total dose of 45–50 Gy, administered in 1.8 Gy fractions (25–30 fractions). Pelvic and para-aortic nodal metastases were treated using the simultaneous integrated boost (SIB) technique, delivering doses of 50–55 Gy and 55–60 Gy, respectively. Concurrent chemotherapy with cisplatin (40 mg/m²) was administered weekly in 93.3% of patients. The mean interval from diagnosis to initiation of radiotherapy was 62.6 days (standard deviation $\pm$ 70.5). An α/β ratio of 10 Gy was used for tumour volumes and an α/β ratio of 3 Gy for organs at risk (OARs).

6.2.3 Post-Therapeutic Follow-Up and Statistical Analysis

Descriptive statistics were used to summarize baseline patient characteristics, dosimetric parameters, and the toxicity profile. Survival outcomes, including LC, PFS, and OS, were estimated using the Kaplan–Meier method.

6.3 Results

6.3.1 Dosimetric Analysis and Treatment Parameters

The cumulative mean D2cm³ EQD2 doses to the bladder, rectum, sigmoid colon, and small bowel were 84.8 Gy (84.0–85.7), 71.4 Gy (70.6–72.1), 66.8 Gy (65.8–67.8), and 62.1 Gy (61.1–63.2), respectively, all remaining within the EMBRACE II protocol planning constraints. The relationship between HR-CTV volume and achieved dose coverage (HR-CTV D90 EQD2), stratified according to FIGO stage (II–IV), is illustrated in Figure 6.1.

Following the individual ROC curve analysis for HR_CTV1, EQD₂ HR-CTV, EQD₂ IR-CTV, and OTT, it was found that among HR-CTV1, EQD₂ HR-CTV, EQD₂ IR-CTV, and OTT, *the only significant predictor was HR-CTV1, suggesting the use of HR-CTV1 as a prognostic factor for survival.*

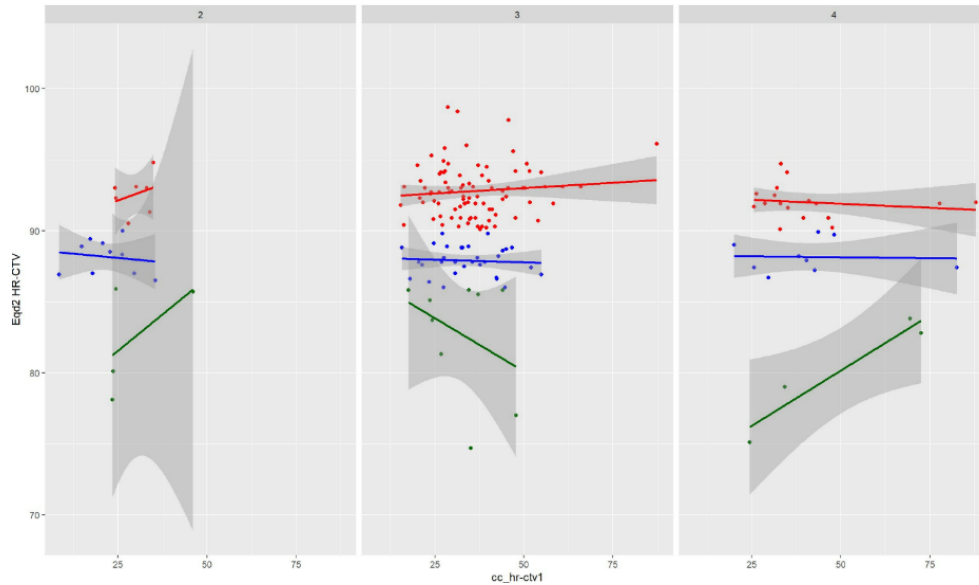


Figure 6.1 Correlation Between HR-CTV Clinical Target Volume and Achieved D90 EQD2 Dose, Stratified According to FIGO Stage (II, III, and IV)

6.3.2 Oncologic Outcomes and Survival

Evaluation of clinical outcomes at different time points, with a 95% confidence level, showed that the probability of survival at 1 year, 2 years, and 5 years was 98.3%, 76.1%, and 61.2%, respectively. Progression-free survival was 90.6% at 1 year, 68.9% at 3 years, and 56.9% at 5 years, while local control remained high, with rates of 98.9% at 1 year and 94.5% at 2 years. *The mortality rate increased as the waiting time increased.*

6.3.3 Prognostic Factors and Statistical Models

Univariate analysis identified several factors that could serve as prognostic predictors associated with reduced survival: histological subtype, FIGO stage, haemoglobin value (HB), histological differentiation grade (G), HR-CTV, and OTT.

The main results of the statistical analysis were as follows: patients with adenocarcinoma (ADK) had significantly lower survival rates; survival decreased as the histological differentiation grade increased; patients had lower chances of survival as the disease became more advanced according to FIGO stage; and patients with severe anaemia, defined as HB below 8 g/dL, had significantly lower survival rates compared with the other subgroups.

6.3.4 General Analysis of Recurrences

Figure 6.2 schematically illustrates the distribution of recurrence according to localization.

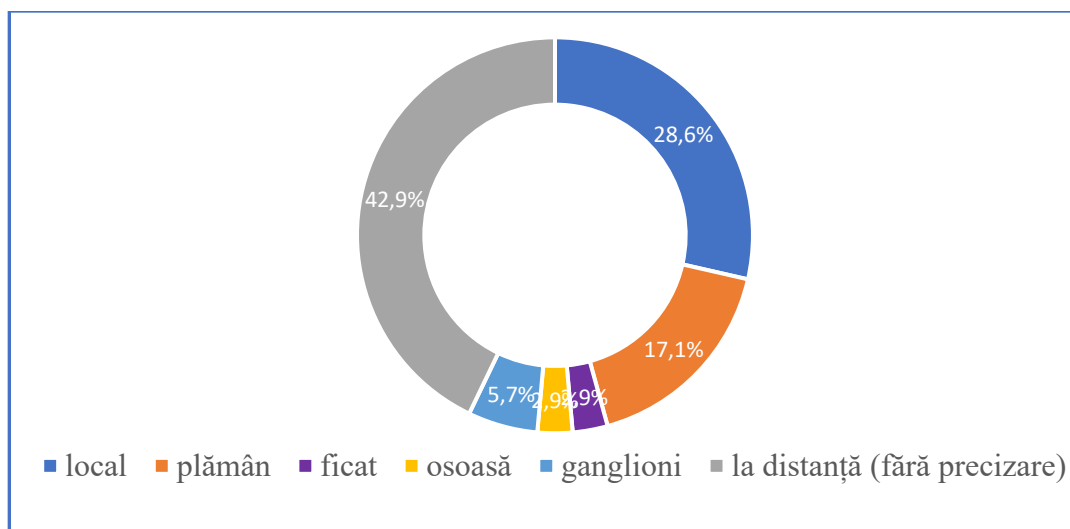


Figure 6.2 Structure of Patients According to Recurrence Localization

The comparison performed across FIGO stages highlighted statistically significant differences in recurrence-free survival ($p = 0.034$). The mean recurrence-free interval was 47.6 months for stage II, 39.7 months for stage III, and 33.2 months for stage IV. At one year, the probability of recurrence-free survival was 95% for women with stage II disease, 86% for stage III, and decreased to 73% for stage IV.

The analysis of recurrence according to comorbidities did not reveal statistically significant differences. SCC histology was not significantly associated with a higher rate of distant recurrence. Age did not show a statistically significant impact on recurrence. However, disease stage was an essential and statistically significant factor, with stage IV patients having an approximately 8-fold higher risk of death compared with stage II patients. Histological type was also identified as a significant predictor of survival.

6.3.5 Multivariate Analysis Using the Cox Regression Model

The overall statistical analysis demonstrated a good ability to adjust for the risk of death.

The presence of recurrence represented the most important negative prognostic factor, increasing the risk of death by 5.8-fold (95% CI: 2.21–15.35; $p < 0.001$). A significant correlation was established between the cumulative irradiation dose, EQD₂ HR-CTV, and mortality (HR = 1.067; $p < 0.001$). Higher values of this parameter appeared to be associated with an increased risk of death.

6.4 Discussion

While stage II cases maintained stable dose coverage, stage IV tumours showed lower EQD₂ values, reflecting the geometric complexity of late-stage disease.

By complementing CT imaging with pre-brachytherapy MRI evaluation for target volume contouring (in 78% of cases), results comparable to those reported in exclusively MRI-guided series were achieved.

6.5 Conclusions

The results confirm the effectiveness of image-guided adaptive brachytherapy combined with chemoradiotherapy (CRT) in the treatment of locally advanced cervical cancer, achieving favourable rates of local control and survival. The analysed clinical and biological factors (FIGO stage, histological type, haemoglobin values, disease recurrence, and HR-CTV) significantly influenced patient prognosis and survival, highlighting the importance of risk stratification and treatment individualization.

The observed acute and late toxicities, particularly vaginal stenosis and pelvic functional impairment, emphasize that therapeutic success should not be evaluated exclusively through tumour control and survival, but also through the burden of treatment on patients' functional status and daily life.

The results presented in this chapter demonstrate the need for further evaluation of the consequences of treatment on daily functioning, overall functionality, and socio-familial reintegration in patients treated for cervical cancer.

7. Longitudinal Evaluation of Quality of Life and Post-Treatment Functional Morbidity

7.1 Introduction

Pelvic radiotherapy, extensive surgical interventions, and systemic treatments may produce structural and functional changes with significant repercussions on daily activity and sexual health. Radiation-induced vaginal morbidity occupies a central place among late complications, including vaginal stenosis, fibrosis, dyspareunia, and impaired tissue elasticity. These changes are frequently associated with reduced sexual activity, altered body image, and impaired interpersonal relationships. In parallel, symptoms such as pelvic pain,

chronic cystitis, fatigue, or lymphedema may further contribute to deterioration of HRQoL. The use of PROMs allows the transformation of patients' subjective experiences into quantifiable data and facilitates the multidimensional assessment of HRQoL.

The present study had the following specific objectives:

- Evaluation of the incidence, severity, and temporal dynamics of late vaginal complications and their consequences on HRQoL;
- Identification of clinical and technical factors influencing vaginal morbidity, sexual dysfunction, and functional implications;
- Predictive identification of clinical factors and dose-effect correlations influencing the occurrence of pelvic adverse effects;
- Quantification of the effect of IGABT treatment on sexual function and quality of life using internationally validated instruments;
- Correlation between dosimetric parameters and morbidity;
- Formulation of practical multidisciplinary recommendations for optimization of BT plans and implementation of functional rehabilitation strategies.

7.2 Patients and methods

The study included a cohort of 180 diagnosed and treated patients, of whom 155 responded to the evaluation, while 24 had died by the end of data collection. Vaginal morbidity was clinically assessed at baseline and at 3, 6, and 12 months using the CTCAE v5.0 criteria. Evaluated parameters included stenosis, vaginal dryness, bleeding, mucositis, and fistula formation.

For the assessment of HRQoL and vaginal toxicity, the internationally validated questionnaires EORTC QLQ-C30 and EORTC QLQ-CX24 were administered at treatment initiation and at 3 and 12 months. The implications of the disease on daily life and cervical cancer-specific symptoms was evaluated, including sexual function, vaginal symptomatology, and body image. The questionnaire completion rate was 91.7%.

Analyses were performed using SPSS v25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized patient characteristics. Categorical variables were compared using chi-square or Fisher's exact tests, while continuous variables were analysed using the Student's t-test or the Mann-Whitney U test. The analysis of results was primarily descriptive, evaluating the frequency of late complications and their distribution within the study cohort.

The results were interpreted in the context of the effect of toxicities on HRQoL and the need for long-term multidisciplinary follow-up of patients treated for cervical neoplasia. To assess the clinical and functional outcome of complications, PROM-specific evaluation principles were applied, allowing integration of the patients' subjective perception of symptoms and treatment effects.

7.3 Results, Discussion

7.3.1 Analysis of Symptoms and Clinical Complications

The evaluation assessed both the objective clinical severity of toxicities and their impact on daily activities, sexual health, body image, and social relationships. Information regarding sexual activity, the use of vaginal dilators, and certain socioeconomic aspects, including financial independence, was also collected.

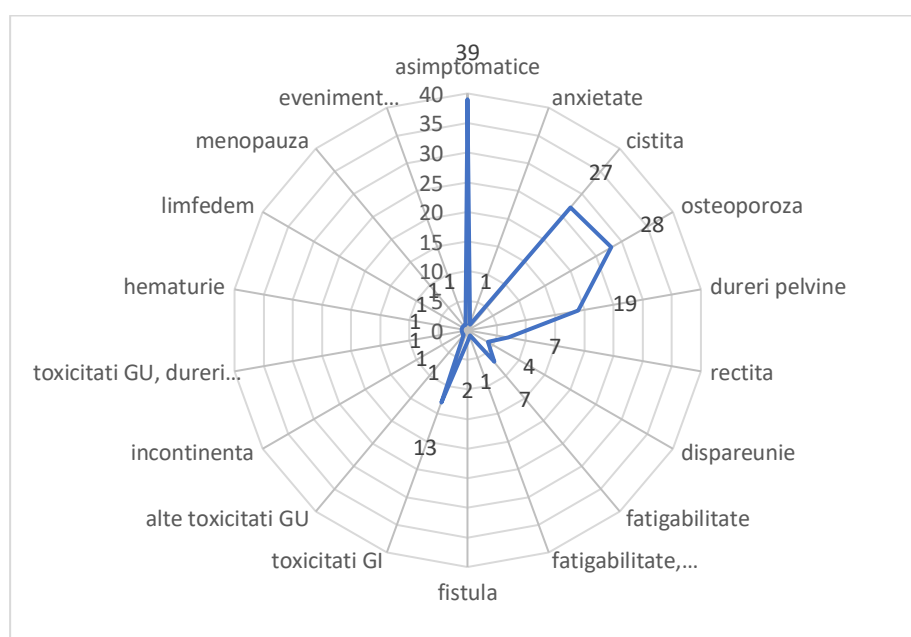


Figure 7.1 Distribution of Dominant Complications

An increased frequency of toxicity was observed in patients who received doses higher than 70 Gy. These results suggest the existence of a dose–effect relationship between irradiation and vaginal morbidity. Figure 7.1 presents the distribution of dominant complications. The increased frequency of osteoporosis, pelvic pain, and gastrointestinal toxicities indicates the persistence of late effects with a significant impact on quality of life, highlighting the need for multidisciplinary

follow-up, including gynaecologic, endocrinologic, rheumatologic evaluation, and functional rehabilitation support.

Regarding radiation-induced vaginal morbidity, vaginal stenosis was identified as the predominant complication among surviving patients, with most presenting grade 1 vaginal stenosis ($n = 72$), while 13 patients developed grade 2 stenosis.

The fact that 7% of surviving patients did not develop vaginal stenosis may reflect the heterogeneity of tissue response to radiotherapy and the influence of protective factors such as delivered dose, irradiation technique, hormonal status, sexual activity, or the use of preventive measures, including vaginal dilators.

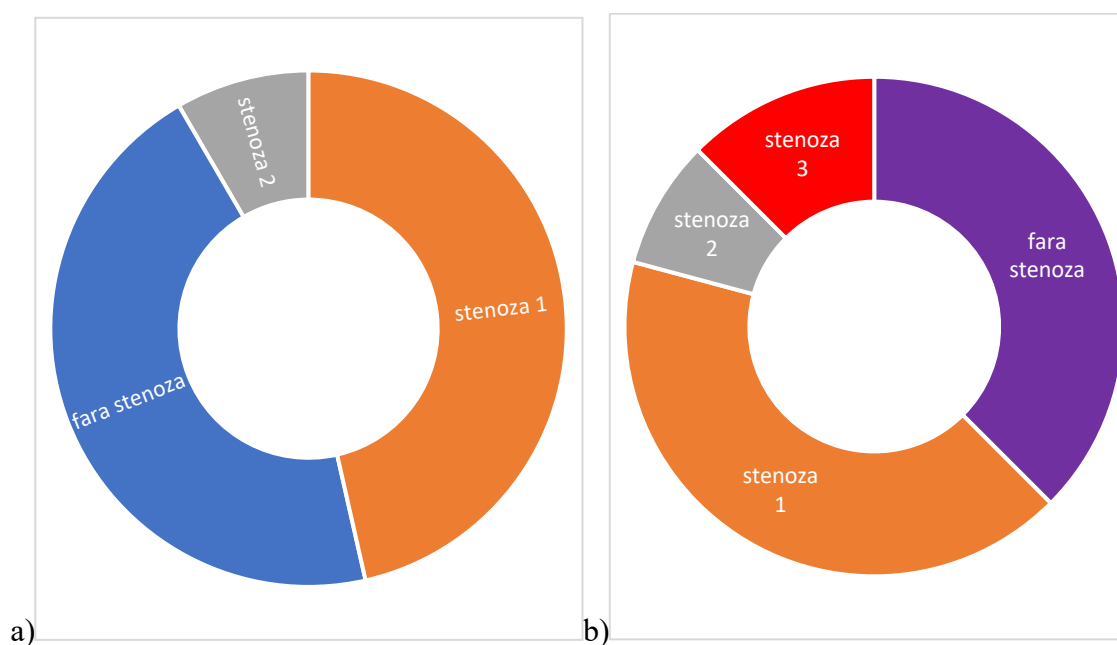


Figure 7.2 Distribution of Stenosis Grades in a) Surviving Patients and b) Deceased Patients

The presence of grade 2 vaginal stenosis in 13 patients suggests the existence of more significant structural changes, with potential impact on gynaecologic examination, oncologic follow-up, and sexual function. Even in the absence of grade 3 stenosis cases among surviving patients, the observed distribution indicates the persistence of clinically relevant vaginal morbidity after oncologic treatment. These late effects are not frequently reported in routine clinical practice, although they significantly influence HRQoL and the psychosexual adaptation of patients.

7.3.2 The Role of PROMs in the Assessment of HRQoL

The results obtained in this study highlight the importance of patient-centered assessment in evaluating the impact of late toxicities on health-related quality of life (HRQoL). The presence of urinary, pelvic, sexual, and musculoskeletal symptoms reported by patients demonstrates that post-therapeutic morbidity cannot be assessed exclusively through objective clinical parameters, making the integration of patients' subjective perceptions into the oncologic follow-up process essential.

Assessment of patient perception through PROMs highlights the major impact of oncologic treatment on quality of life and daily functioning. Symptoms such as pelvic pain, fatigue, dyspareunia, vaginal dryness, and urinary disorders significantly affect sexual health, body image, interpersonal relationships, and social reintegration.

The study demonstrates that exclusively clinical evaluation may underestimate the true severity of these problems, as apparently minor changes may produce significant functional and psychological impairment. In this context, the systematic integration of PROMs into post-therapeutic monitoring enables early identification of late toxicities, improves physician–patient communication, and contributes to the development of patient-centered oncologic care focused not only on survival, but also on optimization of quality of life.

7.3.3 Quality of Life Assessment

7.3.3.1 Analysis of Health-Related Aspects

The administered questionnaires allowed the assessment of individual perceptions regarding health status, exercise tolerance, and long-term functional capacity. The results demonstrated a relative stability of exercise capacity over time, with nearly half of the patients reporting difficulties in performing light physical activities, such as lifting objects. In contrast, most women maintained a good ability to perform short walks, with over 85% reporting minimal effort regardless of the evaluation time point. However, one year after treatment, an increased need for rest and assistance with daily activities was observed, although the proportion of patients with severe dependency remained low.

The ability to perform professional and household activities did not show statistically significant changes throughout the evaluation period. Recreational activities and leisure time, however, showed a heterogeneous evolution: some patients reported improvement, while others

experienced increased limitations at one year. Respiratory complaints remained infrequent throughout follow-up, while pain showed a significant progressive improvement. The proportion of patients without pain nearly doubled at one year compared with baseline evaluation.

Regarding fatigue and the need for rest, a temporary improvement was observed at three months, followed by a slight deterioration at one year, without major differences compared with baseline. Sleep disturbances progressively decreased over time, and the general feeling of weakness showed significant improvement compared with the postoperative period. In addition, appetite steadily improved, with the proportion of patients reporting no eating difficulties increasing significantly at 12 months.

Overall, the results suggest that although many physical symptoms improve after treatment, persistent functional and emotional impairments continue to significantly influence long-term quality of life. These findings support the need for multidimensional patient monitoring and the integration of patient-centred assessments into modern oncologic practice.

The results also revealed an apparently paradoxical evolution in patient perception: over time, both the proportion of women rating their health status as very good or excellent and the proportion perceiving poor health increased. Analysis of mean scores showed that general health status tended to progressively deteriorate, whereas overall quality of life was perceived as increasingly better. The correlation between general health status and quality of life was weak and not statistically significant at all evaluation time points, with the Spearman coefficient decreasing from 0.24 at baseline to approximately 0.07–0.08 at 3 and 12 months.

7.3.3.2 Analysis of Subjective Symptoms

The analysis of subjective symptoms using the EORTC QLQ-CX24 questionnaire highlights the complex evolution of late effects following cervical cancer treatment. Urinary symptoms increased during the first 3 months after treatment; however, at the one-year evaluation, most patients had returned to baseline status. The exception was urinary incontinence, which remained more frequent in the long term. Neurological symptoms, such as tingling and numbness, became more frequent at 12 months compared with baseline. In contrast, vulvovaginal irritation, discharge, and abnormal vaginal bleeding showed a statistically significant progressive improvement, particularly after the first year of follow-up.

Hot flashes and sweating increased in frequency after treatment, suggesting the impact of treatment-induced ovarian insufficiency. Perception of body image, femininity, and personal

attractiveness remained relatively stable, with approximately half of the patients reporting that they did not feel less feminine or less satisfied with their own body.

Regarding sexual health, fear of painful sexual contact significantly decreased after treatment; however, sexual activity progressively declined, with the proportion of sexually inactive patients increasing from 57.2% at baseline to 72.2% at one year. Sexual function deteriorated over time, mainly influenced by vaginal dryness, stenosis, and reduced sexual satisfaction. Approximately one quarter of patients regularly used vaginal dilators or maintained continuous sexual activity, while non-use of vaginal dilators was identified as the main modifiable risk factor for the development of severe vaginal stenosis.

Perception of vaginal narrowing and shortening worsened significantly after treatment, with many patients expressing major concerns related to vaginal stenosis. Although pain during sexual intercourse did not significantly increase at the global statistical level, a proportion of patients reported the development of dyspareunia during late evaluations. Overall, the results highlight the major and persistent impact of radiation-induced toxicities on sexual health and quality of life, emphasizing the importance of monitoring subjective symptoms and implementing long-term supportive interventions.

7.3.4 Clinical and Therapeutic Implications

7.3.4.1 Need for Multidisciplinary Follow-Up

Follow-up of patients treated for cervical cancer requires a multidisciplinary approach, as late toxicities of oncologic treatment simultaneously affect anatomical, physical, and psychosocial functions, significantly influencing quality of life (HRQoL).

Periodic gynecologic evaluation is essential both for recurrence detection and for the early identification of radiation-induced complications such as vaginal stenosis, fibrosis, mucosal atrophy, and sexual dysfunction. In parallel, the radiation oncologist monitors the relationship between delivered doses and the severity of late toxicities, contributing to the optimization of therapeutic strategies and the prevention of severe complications.

Medical rehabilitation also plays an important role in maintaining patient functionality and autonomy through interventions focused on pain control, fatigue management, lymphedema treatment, and improvement of pelvic mobility.

In addition, psychological support and sexological counseling are indispensable for managing anxiety, depression, altered body image, and sexual dysfunction associated with oncologic treatment. The integration of these specialties contributes not only to improved survival, but also to the preservation of functionality, social reintegration, and long-term psychosocial well-being.

7.3.4.2 Prevention and Management of Late Toxicities

The use of vaginal dilators represents one of the principal methods for preventing radiation-induced vaginal stenosis, contributing to the maintenance of vaginal elasticity and patency, although patient compliance is often limited. Sexual counselling also plays an important role in identifying and managing sexual dysfunction and its associated psychological impact, facilitating physician–patient communication and reducing psychosocial impairment.

Symptomatic management includes pharmacologic therapies, physiotherapy, medical rehabilitation, and psychological support for the control of pain, fatigue, and other persistent symptoms. In addition, screening for osteoporosis and lymphedema enables early identification of complications and the prompt initiation of preventive and therapeutic measures. The integration of periodic assessment and PROMs instruments contributes to the adaptation of therapeutic strategies and the optimization of long-term quality of life.

7.3.4.3 Personalization of Oncologic Follow-Up

The increased survival of patients with cervical cancer has led to a redefinition of oncologic follow-up, which must focus not only on recurrence detection, but also on the identification and management of late toxicities and their impact on quality of life (HRQoL). In this context, personalization of post-therapeutic follow-up becomes essential for maintaining long-term functionality and autonomy.

A central role is played by risk stratification, which allows individualized monitoring according to the clinical and therapeutic characteristics of patients. Factors such as total radiotherapy dose, irradiated volumes, the addition of chemotherapy, hormonal status, age, and comorbidities influence the risk of late complications, including vaginal stenosis, sexual dysfunction, urinary disorders, lymphedema, and osteoporosis. Early identification of high-risk patients facilitates the implementation of adapted preventive and therapeutic measures, such as the use of vaginal dilators, sexual counselling, or osteoporosis monitoring.

Periodic evaluation should include both oncologic status and urinary, gastrointestinal, sexual, and psychological symptoms through a multidisciplinary approach involving the oncologist, radiation oncologist, gynaecologist, rehabilitation specialist, and psychologist.

The integration of HRQoL assessment and PROMs instruments into clinical practice enables direct evaluation of the patient's perception of symptoms and the impact of treatment on daily life. These instruments contribute to identifying underreported problems, such as sexual dysfunction, anxiety, or altered body image, and facilitate the individualization of therapeutic strategies. Thus, modern oncologic success should not be defined solely by survival and tumour control, but also by the preservation of a quality of life as close to normal as possible.

7.4 Conclusions

The longitudinal data demonstrated a significant improvement in pain, fatigue, and sleep disturbances following IGABT, as well as an improvement in overall quality of life, mainly driven by symptom reduction. However, physical and sexual function remained impaired, highlighting that global quality-of-life indicators do not fully reflect the functional impact of treatment.

Non-use of vaginal dilators represented the most important independent modifiable predictor of grade ≥ 2 vaginal stenosis, supporting the need for standardized implementation of vaginal rehabilitation programs and dedicated counselling, particularly in postmenopausal patients.

The study demonstrates the importance of integrated assessment of symptoms, toxicities, and patients' subjective perceptions using PROMs and HRQoL instruments. The results support the need for multidisciplinary follow-up and for strategies aimed at the prevention and early management of late toxicities, with the goal of optimizing functional survivorship and long-term quality of life.

8. CONCLUSIONS

This doctoral research demonstrated that CT-guided adaptive brachytherapy represents an effective and feasible method for the treatment of patients with locally advanced cervical cancer, allowing the achievement of a favourable balance between oncologic control and limitation of late toxicities. The use of hybrid intracavitary–interstitial techniques enabled the delivery of high tumoricidal doses while respecting dosimetric constraints for organs at risk, even in a cohort with

unfavourable prognosis characterized by advanced FIGO stages, bulky tumours, and frequent nodal involvement.

The analysis of clinical and functional outcomes revealed a low rate of severe vaginal stenosis, with a predominance of mild and moderate forms amenable to prevention and rehabilitation. At the same time, the study demonstrated that vaginal morbidity and sexual dysfunction remain important components of late toxicity, with significant impact on daily functioning, personal relationships, and the emotional status of surviving patients.

Prospective evaluation of quality of life using the internationally validated EORTC QLQ-C30 and CX24 instruments demonstrated improvement in general symptoms and overall perception of health status after treatment, together with the persistence of progressive deterioration in sexual function in some patients. The results confirm the existence of a dissociation between oncologic success and complete functional recovery, emphasizing the need to integrate functional and sexual assessments into standard post-therapeutic follow-up.

The study enabled the identification of independent predictive factors for the development of late vaginal morbidity, including age over 55 years, preexisting menopause, large tumour volumes, and non-use of vaginal dilators after treatment. Non-use of vaginal dilators was significantly associated with an increased risk of vaginal stenosis, highlighting the importance of early implementation of preventive measures and functional rehabilitation strategies.

The obtained results support the need for systematic integration of vaginal assessment and PROMs instruments into modern oncologic practice, since the impact of late toxicities frequently exceeds the limits of objective clinical evaluation. By correlating clinical, dosimetric, and functional data, the research proposes a multidisciplinary and patient-centred approach for the evaluation of therapeutic outcomes following IGABT.

From a techno-economic perspective, the study demonstrates that the use of CT guidance represents an accessible and effective alternative for the implementation of adaptive brachytherapy in centres without permanent access to planning MRI. At the same time, the application of modern IGABT techniques requires advanced infrastructure, dedicated software, and specialized medical personnel, factors that may limit the uniform expansion of these technologies in resource-limited centres

Current limitations remain related to the lack of international consensus regarding vaginal contouring on CT imaging and the definition of the exact dose–effect relationship at the level of

the vaginal mucosa. The principal limitations of the technique are associated with the inferior soft tissue contrast of CT compared with MRI, particularly for the precise delineation of residual tumour extension and vaginal walls. This aspect requires advanced clinical expertise and multimodal imaging correlation. In this context, prospective multicentre studies with extended follow-up periods are needed, together with the development of standardized protocols for vaginal protection and functional rehabilitation.

The practical value of this research lies in the immediate applicability of the obtained results, which enabled refinement of irradiation techniques and the formulation of personalized therapeutic strategies simultaneously aimed at optimizing oncologic control, reducing late morbidity, and improving functional survivorship and quality of life in patients treated for locally advanced cervical cancer.

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List of published scientific papers

1. Optimizing Palliative Pelvic Radiotherapy in Gynecological Cancers: A Systematic Review and Analysis.

Beatrice Anghel, Mihai-Teodor Georgescu, Crenguța Sorina Șerboiu, Andreea Nicoleta Marinescu, Cătălin Aliuș, Dragoș-Eugen Georgescu, Bogdan Mocanu, Sabina Sucuri, Anca Daniela Stănescu.

Diagnostics, anul 2024; Vol. 14 (Issue 5): 547.

IF (JCR 2023): 3.4, Q2

Link: <https://doi.org/10.3390/diagnostics14050547>

The article was compiled using the information presented in the 1st chapter (pp. 12-22).

2. *Recent Advances and Adaptive Strategies in Image Guidance for Cervical Cancer Radiotherapy.*

Beatrice Anghel, Crenguța Șerboiu, Andreea Marinescu, Iulian-Alexandru Taciuc, Florin Bobîrcă, Anca Daniela Stănescu.

Medicina, anul 2023; Vol. 59 (Issue 10): 1735.

IF (JCR 2023): 2.6, Q3

Link: <https://doi.org/10.3390/medicina59101735>

The article was compiled using the information presented in the 2nd chapter (pp. 23-31).

3. *Adaptive Target Volume and Dosimetry in Image – Guided Radiotherapy for Cervical Cancer.*

Beatrice Anghel, Elena Manea, Anca Daniela Stănescu, Ana Maria Rață, Bogdan Gafton, Viorel Scripcariu.

J. Clin. Med., anul 2025; 14(10): 3418.

IF (JCR 2023): 3.2, Q2

Link: <https://doi.org/10.3390/jcm14103418>

The article was compiled using the information presented in the 6th chapter (pp. 49-75).