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# Vaginal Morbidity and Quality of Life after CT-Guided Hybrid Brachytherapy for Locally Advanced Cervical Cancer

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## Rezumat

***Morbiditatea vaginală și calitatea vieții după brahiterapia hibridă ghidată CT pentru cancerul de col uterin avansat local***

*Context:* Morbiditatea vaginală post-brahiterapie pentru cancerul de col uterin local avansat (LACC) este frecventă, dar insuficient caracterizată în contextul ghidajului CT. Studiul a evaluat toxicitatea vaginală, calitatea vieții şi predictorii stenozei grad ≥ 2 într-o cohortă prospectiv menținută tratată cu IGABT hibridă CT.
*Metode:* Am analizat retrospectiv o bază de date menținută prospectiv cu 180 paciente LACC (FIGO IB1–IVA) tratate prin chimioradioterapie şi brahiterapie hibridă ghidată CT la Spitalul Clinic SANADOR (2020-2022). Toxicitatea vaginală a fost gradată conform CTCAE v5.0; calitatea vieții a fost evaluată prin EORTC QLQ-C30 şi QLQ-CX24 la momentele baseline, 3 luni şi 12 luni.
*Rezultate:* Înainte de evaluarea toxicității la 12 luni, 15 paciente au fost censurate (10 recurențe, 5 decese), rămânând 165 paciente evaluabile. Toxicitatea severă compozită CTCAE grad ≥ 3 a apărut la 9/165 (5,5%) paciente evaluabile. Stenoza vaginală grad 3 a fost observată la 48/165 paciente evaluabile (29,1%), corespunzând la 48/155 paciente cu stenoză de orice grad (31,0%). Calitatea globală a vieții s-a îmbunătățit semnificativ la 12 luni ($p < 0,05$), în timp ce funcția sexuală a înregistrat un declin progresiv.
*Concluzii:* IGABT hibridă CT a fost asociată cu un control tumoral favorabil; totuşi, deşi toxicitatea vaginală severă compozită a apărut la 9/165 (5,5%) paciente evaluabile, stenoza vaginală grad 3 a fost prezentă la 48/165 (29,1%) paciente evaluabile - aspect care trebuie interpretat separat față de rata toxicității compozite. Există o discrepanță clinic semnificativă între îmbunătățirea calității globale a vieții şi declinul funcției sexuale, subliniind necesitatea unor programe structurate de reabilitare vaginală după IGABT.

**Cuvinte cheie:** cancer de col uterin, brahiterapie, toxicitate vaginală, calitatea vieții,

brahiterapie ghidată CT, brahiterapie adaptativă ghidată imagistic (IGABT), disfuncție sexuală, stenoză vaginală, supraviețuire

## Abstract

*Background:* Vaginal morbidity after brachytherapy for locally advanced cervical cancer (LACC) is frequent but inadequately characterised in CT-guided settings. This study examined vaginal toxicity, quality of life (QoL), and predictors of grade ≥ 2 stenosis in a prospectively maintained CT-guided hybrid image-guided adaptive brachytherapy (IGABT) cohort.

*Methods:* A cohort of 180 LACC patients (FIGO 2018 IB1–IVA) treated with chemoradiotherapy and CT-based hybrid brachytherapy at SANADOR Clinical Hospital (2020-2022) was analysed retrospectively. Vaginal toxicity was graded using CTCAE v5.0; QoL was assessed with EORTC QLQ-C30 and QLQ-CX24 at baseline, 3 months, and 12 months. Exploratory logistic regression identified predictors of grade ≥ 2 stenosis.

*Results:* Before the 12-month toxicity assessment, 15 patients were censored (10 due to recurrence, 5 due to death), leaving 165 evaluable patients. Among these, overall composite CTCAE grade ≥ 3 vaginal toxicity occurred in 9/165 (5.5%). These findings must be interpreted separately from anatomically graded stenosis: 155/165 evaluable patients (93.9%) had any degree of vaginal stenosis at 12 months, and grade 3 stenosis was observed in 48/165 evaluable patients (29.1%), corresponding to 48/155 patients with any stenosis (31.0%). Global QoL improved significantly at 12 months ($p < 0.05$), driven by pain and fatigue reduction, whereas sexual function declined progressively. Non-use of vaginal dilators (OR 3.1, 95% CI 1.4-6.8) and menopausal status (OR 2.4, 95% CI 1.1-5.1) independently predicted grade ≥2 stenosis. HR-CTV D90 $EQD_2$ strongly predicted survival ($p < 0.001$).

*Conclusions:* CT-guided hybrid IGABT was associated with favourable tumour control. Composite CTCAE grade ≥ 3 vaginal toxicity occurred in 9/165 evaluable patients (5.5%) at 12 months; however, grade 3 vaginal stenosis on clinical examination was observed in 48/165 evaluable patients (29.1%), corresponding to 48/155 patients with any stenosis (31.0%) - a finding that must be clearly distinguished from the composite rate and communicated transparently to patients. A clinically meaningful dissociation between improving global QoL and declining sexual function underscores the need for structured vaginal rehabilitation programmes after IGABT.

**Keywords:** cervical cancer, brachytherapy, vaginal toxicity, quality of life, CT-guided brachytherapy, IGABT, sexual dysfunction, vaginal stenosis, survivorship

## Introduction

The standard treatment for locally advanced cervical cancer (LACC) combines external beam radiotherapy with concurrent chemotherapy (CRT) followed by brachytherapy. The introduction of image-guided adaptive brachytherapy (IGABT) has substantially improved local control and survival, as demonstrated in the RetroEMBRACE and EMBRACE-I studies (1-4). However, treatment-related morbidity - particularly vaginal toxicity - remains a major survivorship concern that is incompletely characterised in real-world CT-based cohorts (5,6).

MRI-guided brachytherapy is the recommended standard, yet CT-guided brachytherapy remains the dominant global practice due to MRI cost, availability, and institutional capacity constraints (5,7). Despite this, retrospective outcome data from CT-guided cohorts - particularly for vaginal morbidity and patient-reported quality of life (QoL) - are scarce. Epidemiologically, cervical cancer remains the fourth most common cancer in women worldwide (8), and most patients are treated in settings where MRI guidance is not routinely available.

Vaginal morbidity after IGABT encompasses stenosis, dryness, dyspareunia, bleeding, and fistula formation. The EMBRACE-I study established vaginal stenosis as the predominant late complication, present in most patients, with dose and dilator use identified as significant determinants (6,9,10). However, vaginal dose reporting in CT-based settings is problematic due to the absence of validated contouring protocols and frequent upper vaginal tumour involvement, limiting direct applicability of MRI-derived dose-effect relationships (5,11).

Patient-reported sexual outcomes are frequently dissociated from clinician-graded toxicity scores. Physician assessments tend to underestimate the functional and psychosocial burden of vaginal morbidity (12), particularly in women with mild-to-moderate structural changes that nonetheless significantly impair sexual quality of life (13). Low rates of vaginal dilator use in clinical practice further compound the risk of irreversible stenosis (14,15).

The present study addresses three specific evidence gaps: (1) the scarcity of prospectively collected vaginal morbidity data from CT-guided IGABT cohorts; (2) the absence of longitudinal patient-reported sexual function data from real-world settings; and (3) limited evidence on modifiable predictors of vaginal stenosis outside MRI-guided series. We report the incidence, severity, and temporal evolution of vaginal morbidity, patient-reported QoL, and exploratory predictors of grade ≥ 2 stenosis in one of the larger retrospective CT-based IGABT cohorts published to date.

## Materials and Methods

### *Study Design and Patient Selection*

This is a retrospective observational study analysing a prospectively maintained database, conducted at SANADOR Clinical Hospital, Bucharest, Romania. Consecutive LACC patients with FIGO 2018 stage IB3–IVA treated between January 2020 and December 2022 were enrolled. Four patients with radiologically confirmed para-aortic nodal metastasis, previously labelled as FIGO IVB in the institution's database, were reclassified as FIGO IIIC2 in accordance with the revised FIGO 2018 staging criteria (16), under which para-aortic nodal involvement without distant organ metastasis is classified as stage IIIC2. These patients were treated with curative-intent extended-field radiotherapy (EFRT) following multidisciplinary tumour board review confirming no systemic disease and adequate performance status (ECOG 0-1).

### *Inclusion and Exclusion Criteria*

Inclusion criteria: histologically confirmed cervical cancer; planned curative-intent CRT followed by brachytherapy; ECOG performance status 0-2; written informed consent. Patients with prior pelvic radiotherapy or incomplete treatment were excluded.

### *Ethics*

Patient data were collected prospectively during the treatment and follow-up period. The retrospective analysis of the accumulated database was approved by the Sanador Clinical Hospital Committee of Ethics and Clinical Trials on 27 March 2023, prior to data analysis. All data were anonymised before analysis. QoL questionnaires, including items on sexual function, were administered individually by a dedicated research nurse in a private, confidential setting. Median follow-up was 24.6 months (IQR: 18.3-32.1). The study was conducted in accordance with the Declaration of Helsinki.

### *Treatment*

All patients received EBRT to 45-50 Gy in 25-30 fractions with concurrent cisplatin-based chemotherapy. Para-aortic nodal irradiation (EFRT) was performed in 23 patients using simultaneous integrated boost (SIB) or sequential extended-field technique, including the four FIGO IIIC2 patients with para-aortic involvement. Brachytherapy was delivered using CT-based hybrid intracavitary/interstitial (IC/

**Table 1.** Vaginal toxicity rates by endpoint and grade at each assessment time point

| Endpoint | Acute (during BT) (N = 180) | 3 months (N = 180) | 6 months (N = 180) | 12 months (N = 165) [b] |
|---|---|---|---|---|
| **A. Overall composite CTCAE grade ≥ 3 toxicity (all vaginal endpoints combined)** | | | | |
| Grade ≥ 3 (composite) | 4/180 (2.2%) | 7/180 (3.9%) | 13/180 (7.2%) | 9/165 (5.5%) [b] |
| **B. Vaginal stenosis (anatomically graded by direct clinical examination)** | | | | |
| Any stenosis (grade ≥ 1) | n/a | 112/180 (62.2%) | 140/180 (77.8%) | 155/165 (93.9%) [b] |
| Grade 1 — mild | n/a | 68/180 (37.8%) | 68/180 (37.8%) | 67/165 (40.6%) [b] |
| Grade 2 — moderate | n/a | 32/180 (17.8%) | 40/180 (22.2%) | 40/165 (24.2%) [b] |
| Grade 3 — severe [a,b] | n/a | 11/180 (6.1%) | 25/180 (13.9%) | 48/165 (29.1%); 48/155 (31.0%) [a,b] |
| **C. Other vaginal endpoints** | | | | |
| Vaginal bleeding — any grade | 50/180 (27.8%) | 22/180 (12.2%) | 14/180 (7.8%) | 9/165 (5.5%) [b] |
| Vaginal bleeding — grade ≥ 3 | 4/180 (2.2%) | 2/180 (1.1%) | 2/180 (1.1%) | 1/165 (0.6%) [b] |
| Vaginal dryness — any grade | n/a | 99/180 (55.0%) | 110/180 (61.1%) | 96/165 (58.2%) [b] |
| Vaginal mucositis — any grade | 32/180 (17.8%) | 16/180 (8.9%) | 9/180 (5.0%) | 5/165 (3.0%) [b] |
| Fistula (any) | 0/180 (0.0%) | 2/180 (1.1%) | 4/180 (2.2%) | 7/165 (4.2%) [b] |

[a] Grade 3 stenosis is reported relative to both the evaluable population (48/165, 29.1%) and the stenosis-positive population (48/155, 31.0%). Grade 3 stenosis: severe vault shortening and/or obliteration on direct clinical examination (CTCAE v5.0). This endpoint is distinct from composite grade ≥3 toxicity (Panel A). [b] Before the 12-month assessment, 15 patients were censored: 10 due to disease recurrence and 5 due to death (165 evaluable). BT, brachytherapy; CTCAE, Common Terminology Criteria for Adverse Events v5.0; n/a, not assessed at this time point.

IS) applicators in 4-5 HDR fractions (5.5-6 Gy per fraction) within 2 weeks of EBRT completion.

### *Toxicity Assessment*

Vaginal morbidity was assessed at baseline, 3, 6, and 12 months using CTCAE v5.0 (17). Evaluated endpoints included stenosis (anatomically graded by direct clinical examination), bleeding, dryness, mucositis, and fistula. Two distinct metrics are reported throughout this manuscript and must not be conflated: (1) overall composite CTCAE grade ≥ 3 toxicity, which aggregates all vaginal endpoints referenced to the evaluable population; and (2) anatomically graded vaginal stenosis, graded by direct clinical examination and reported in Panel B of *Table 1* with both the evaluable-population denominator (48/165, 29.1%) and the stenosis-positive denominator (48/155, 31.0%).

Vaginal dose parameters were not reported systematically. CT-based delineation cannot reliably contour vaginal wall structures when tumour involves the upper vaginal third — documented in 86.1% of this cohort (5). A descriptive comparison of available surrogate variables is presented in *Table S1.*

### *Patient-Reported Outcomes*

QoL was assessed using EORTC QLQ-C30 (18) and QLQ-CX24 (17) at baseline, 3 months, and 12 months. Questionnaire completion rates were 98.3%, 94.4%, and 85.6% at baseline, 3, and 12 months, respectively (overall 91.7%). Questionnaires were administered in paper format by a dedicated research nurse. QoL assessments were censored at date of disease recurrence. The QLQ-CX24 is validated for use in cervical cancer populations (19,20).

### *Statistical Analysis*

The primary study endpoint was the incidence and grade of vaginal morbidity at 12 months. Secondary endpoints included overall survival (OS), local control (LC), progression-free survival (PFS), and longitudinal patient-reported QoL. All analyses are exploratory; results should be interpreted as hypothesis-generating.

Descriptive statistics summarised patient characteristics. Categorical variables were compared using chi-square or Fisher's exact tests; continuous variables by Student's t-test or Mann–Whitney U test. Missing QoL data were handled by last-observation-carried-forward (LOCF) for sensitivity analyses only; primary analyses used available data. McNemar's test compared proportions at each time point; continuous QoL changes were assessed using the Wilcoxon signed-rank test with Bonferroni correction (threshold $p < 0.017$ for three time-point comparisons).

Time-to-event outcomes were estimated using Kaplan–Meier analysis; group differences assessed by log-rank test. Multivariable Cox proportional hazards models for OS and LC included a priori covariates: FIGO stage, HR-CTV D90 $EQD_2$, radiological nodal status, and tumour size. The proportional hazards assumption was assessed graphically using log-log survival plots; no major violations were identified for primary covariates, although formal residual-based testing was not performed and minor violations cannot be excluded.

An exploratory logistic regression for grade ≥ 2 vaginal stenosis at 12 months was constructed using five predictors: age (> 50 vs ≤ 50 years), menopausal status, smoking, FIGO stage (IIIC–IVA vs IB–IIIB), and vaginal dilator use (regular vs none). The effective events-per-variable (EPV) was approximately 20, adequate for exploratory modelling but insufficient for definitive estimation. Model fit was assessed by the Hosmer–Lemeshow test. All p-values are two-sided. Analyses were performed using SPSS v25.0 (IBM Corp., Armonk, NY, USA); $p < 0.05$ was considered statistically significant.

## Results

### *Patient Characteristics and Follow-Up*

One hundred eighty consecutive patients were enrolled. Baseline characteristics are presented in *Table 2*. Median age was 54 years (IQR: 46–63). Most patients had FIGO stage IIIC1–IIIC2 disease (67.8%), squamous cell carcinoma histology (88.3%), and radiologically positive nodal status (82.8%). Tumour size was ≥50 mm in 56.7%. Tumour involvement of the upper vaginal third at brachytherapy was documented in 86.1%. Of 180 enrolled patients, 165 (91.7%) completed at least one post-baseline QoL assessment and were included in longitudinal analyses. Before the 12-month toxicity assessment, 15 patients were censored: 10 due to disease recurrence and 5 due to death, leaving 165 evaluable patients for 12-month toxicity analyses.

### *Survival and Oncologic Outcomes*

Kaplan–Meier survival estimates are summarised in *Tables 3 A, B.* Mean OS was 48.1 months (95% CI: 44.9–51.3) for stage II, 40.2 months (95% CI: 37.9–42.4) for stage III, and 34.4 months (95% CI: 29.6–39.2) for stage IV (log-rank $p = 0.034$). LC was

**Table 2.** Patient and tumour characteristics (N = 180).

| Variable | Category | N | % |
|---|---|---|---|
| Age (years) | ≤ 50 | 77 | 42.8 |
| | > 50 | 103 | 57.2 |
| FIGO Stage (2018) | IB–IIB | 21 | 11.7 |
| | IIIA–IIIB | 7 | 3.9 |
| | IIIC1–IIIC2 [a] | 122 | 67.8 |
| | IVA | 30 | 16.7 |
| Histology | Squamous cell carcinoma | 159 | 88.3 |
| | Adenocarcinoma | 13 | 7.2 |
| | Other | 8 | 4.4 |
| Tumour size | <50 mm | 78 | 43.3 |
| | ≥ 50 mm | 102 | 56.7 |
| Nodal status | Radiologically positive | 149 | 82.8 |
| | Negative | 31 | 17.2 |
| Brachytherapy | IC only | 89 | 49.4 |
| | IC/IS hybrid | 91 | 50.6 |
| Vaginal involvement | Upper third involved at BT | 155 | 86.1 |
| | Not involved | 25 | 13.9 |
| Smoking | Active smoker | 90 | 50.0 |
| Menopausal status | Postmenopausal | 98 | 54.4 |

[a] IIIC2 includes patients with para-aortic nodal metastasis (n = 4) who were reclassified from the previous label "IVB" in accordance with FIGO 2018 staging criteria, under which para-aortic nodal involvement without distant organ metastasis is classified as stage IIIC2. These patients were treated with curative-intent extended-field radiotherapy following multidisciplinary tumour board review confirming no systemic disease and adequate performance status (ECOG 0–1). BT: brachytherapy; IC: intracavitary; IS: interstitial; FIGO: International Federation of Gynecology and Obstetrics.

98.9% (95% CI: 97.3–100%) at 1 year and 94.5% (95% CI: 91.1–98.1%) at 2 years. During follow-up, 28 deaths, 10 local failures, and 38 PFS events occurred; 152 patients were censored at last contact. On multivariable Cox analysis, higher HR-CTV D90 $EQD_2$ was independently associated with improved OS (HR 0.94, 95% CI 0.91–0.97, $p < 0.001$) and LC (HR 0.88, 95% CI 0.83–0.94, $p < 0.001$). FIGO stage IIIC–IVA was associated with worse OS (HR 2.31, 95% CI 1.18–4.52, $p = 0.014$). Full multivariable results and absolute event counts are presented in *Tables 3 A,B*.

### *Dosimetric Outcomes*

Mean cumulative $EQD_2$ D2 $cm^3$ doses to the bladder, rectum, sigmoid, and bowel were 84.8 Gy (95% CI 84.0–85.7), 71.4 Gy (95% CI 70.6–72.1), 66.8 Gy (95% CI 65.8–67.8), and 62.1 Gy (95% CI 61.1–63.2), respectively (*Table 4*). All values remained within EMBRACE II safety constraints (21,22).

### *Vaginal Toxicity*

*Table 1* presents vaginal toxicity rates by endpoint and grade at each assessment time point. Two distinct metrics are reported: composite CTCAE grade ≥3 toxicity (Panel A) and anatomically graded vaginal stenosis (Panel B). Before the 12-month assessment, 15 patients were censored (10 recurrences, 5 deaths), leaving 165 evaluable patients. Among these, overall composite CTCAE grade ≥ 3 vaginal toxicity occurred in 9/165 (5.5%).

These composite results must be distinguished from anatomically graded stenosis. Among 165 evaluable patients at 12 months, 155 (93.9%) had any degree of vaginal stenosis. Grade 3 stenosis was

**Table 3 A.** Multivariable Cox proportional hazards analysis: overall survival (OS) and local control (LC). N = 180; median follow-up 24.6 months (IQR 18.3–32.1).

| Variable | OS HR | OS 95% CI | p | LC HR (95% CI) | p |
|---|---|---|---|---|---|
| HR-CTV D90 $EQD_2$ (per Gy) | 0.94 | 0.91–0.97 | <0.001 | 0.88 (0.83–0.94) | <0.001 |
| FIGO stage IIIC–IVA vs IB–IIIB | 2.31 | 1.18–4.52 | 0.014 | 1.74 (0.89–3.41) | 0.106 |
| Nodal status (pos vs neg) | 1.42 | 0.68–2.96 | 0.349 | 1.19 (0.54–2.60) | 0.661 |
| Tumour size (per 10 mm) | 1.09 | 0.97–1.22 | 0.143 | 1.04 (0.91–1.18) | 0.571 |
| Disease recurrence | 5.87 | 3.12–11.04 | <0.001 | — | — |

HR, hazard ratio; CI, confidence interval; OS, overall survival; LC, local control; $EQD_2$, equivalent dose in 2 Gy fractions.

**Table 3 B.** Absolute oncologic event counts (N = 180).

| Outcome | Events n (%) | 1-year rate (95% CI) | 2-year rate (95% CI) |
|---|---|---|---|
| Overall survival — deaths | 28/180 (15.6%) | 93.1% (88.6–97.6%) | 84.4% (78.2–90.6%) |
| Local control — failures | 10/180 (5.6%) | 98.9% (97.3–100%) | 94.5% (91.1–98.1%) |
| Progression-free survival — events | 38/180 (21.1%) | 88.3% (83.2–93.4%) | 78.9% (72.6–85.2%) |
| Censored (OS analysis, event-free) | 152/180 (84.4%) | — | — |

Events are non-overlapping except where indicated. Local failures are a subset of PFS events.

**Table 4.** Cumulative doses to organs at risk (EBRT + brachytherapy, $EQD_2$, $\alpha/\beta$ = 3 Gy).

| OAR | Mean D2 $cm^3$ $EQD_2$ (Gy) | 95% CI (Gy) | EMBRACE II Constraint |
|---|---|---|---|
| Bladder | 84.8 | 84.0–85.7 | < 90 Gy |
| Rectum | 71.4 | 70.6–72.1 | < 75 Gy |
| Sigmoid | 66.8 | 65.8–67.8 | < 75 Gy |
| Bowel | 62.1 | 61.1–63.2 | < 70 Gy |

$EQD_2$: equivalent dose in 2 Gy fractions; D2 $cm^3$: minimum dose to the most irradiated 2 $cm^3$; OAR: organ at risk; CI: confidence interval.

**Table 5.** Exploratory logistic regression: predictors of grade ≥ 2 vaginal stenosis at 12 months (n = 165 evaluable).

| Predictor | OR | 95% CI | p-value |
|---|---|---|---|
| Menopausal status (post vs. pre) | 2.4 | 1.1–5.1 | 0.027 |
| No vaginal dilator use (none vs. regular) | 3.1 | 1.4–6.8 | 0.004 |
| Age >50 years | 1.8 | 0.9–3.6 | 0.091 |
| FIGO stage IIIC–IVA (vs. IB–IIIB) | 1.6 | 0.8–3.3 | 0.188 |
| Active smoking | 1.3 | 0.6–2.6 | 0.452 |

OR: odds ratio; CI: confidence interval. Hosmer–Lemeshow goodness-of-fit p = 0.43. Results are exploratory; no correction for multiple testing applied. Reference categories: premenopausal, regular dilator use, age ≤ 50, stage IB–IIIB, non-smoker.

observed in 48/165 evaluable patients (29.1%), corresponding to 48/155 patients with any stenosis (31.0%). Acute vaginal bleeding during brachytherapy occurred in 50/180 (27.8%), with grade ≥3 events in 4/180 (2.2%). Fistula formation was observed in 7/165 (4.2%) evaluable patients at 12 months. Vaginal bleeding and mucositis were predominantly grade 1 and declined progressively over time. A descriptive surrogate analysis is presented in *Table S1.*

### *Predictors of Grade ≥ 2 Vaginal Stenosis: Exploratory Analysis*

In the exploratory logistic regression, menopausal status (OR 2.4, 95% CI 1.1-5.1, p = 0.027) and non-use of vaginal dilators (OR 3.1, 95% CI 1.4-6.8, p = 0.004) were independently associated with grade ≥ 2 stenosis at 12 months. Age >50 years showed a trend toward significance (OR 1.8, 95% CI 0.9-3.6, p = 0.091). FIGO stage and smoking were not independently significant. Hosmer-Lemeshow goodness-of-fit: p = 0.43. Results are presented in *Table 5.*

### *Sexual Function and Rehabilitation*

Among 180 patients, 43 (23.9%) reported regular vaginal dilator use at the 12-month follow-up visit; 44 (24.4%) reported ongoing sexual activity. For the purpose of analysis, regular dilator use was operationally defined as use at least three times per week for a minimum of 10 minutes per session. Patients were generally advised to initiate use approximately 4 weeks after brachytherapy completion; however, counselling was not delivered according to a formal written protocol, and adherence was self-reported at follow-up visits (14,15). Sexual functioning scores (QLQ-CX24 subscales) declined progressively over 12 months. Among sexually active patients, vaginal dryness and dyspareunia were the most frequently reported barriers at 12 months.

### *Quality of Life and Functional Outcomes*

Longitudinal QoL data are presented in *Table 6.* Pain improved significantly between baseline and 12 months (32/165 (19.4%) vs 56/141 (39.4%) reporting no or minimal pain; p < 0.001). Fatigue and sleep disturbance also improved. After Bonferroni correction, improvements in pain (p < 0.001) and fatigue (p = 0.003) retained significance; sleep improvement did not (p = 0.04). Physical functioning declined: the proportion reporting no need to rest during the day fell from 75/165 (45.5%) at baseline to 47/141 (33.3%) at 12 months (p = 0.031). Global QoL improved overall. Among sexually active patients (n = 44), the proportion reporting no dyspareunia fell from 18/44 (40.9%) at baseline to 10/44 (22.7%) at 12 months (p = 0.009).

**Table 6.** Longitudinal patient-reported quality-of-life outcomes (N = 165 longitudinal set).

| Domain (EORTC QLQ-C30 / CX24) | Baseline (n = 165) | 3 months (n = 156) | 12 months (n = 141) | p-value [a] |
|---|---|---|---|---|
| No/minimal pain (QLQ-C30) | 32/165 (19.4%) | 44/156 (28.3%) | 56/141 (39.4%) | <0.001* |
| No fatigue (QLQ-C30) | 51/165 (31.1%) | 69/156 (44.2%) | 69/141 (48.9%) | 0.003* |
| No sleep disturbance (QLQ-C30) | 63/165 (38.3%) | 77/156 (49.4%) | 74/141 (52.5%) | 0.04 |
| No need to rest during day (QLQ-C30) | 75/165 (45.5%) | 61/156 (39.1%) | 47/141 (33.3%) | 0.031 |
| Global QoL ≥ 60 (QLQ-C30) | 73/165 (44.2%) | 81/156 (51.9%) | 83/141 (58.9%) | 0.012* |
| Sexual activity reported (CX24) | 43/165 (26.1%) | 39/156 (25.0%) | 34/141 (24.1%) | 0.78 |
| No dyspareunia (CX24, active pts) [b] | 18/44 (40.9%) | 14/44 (31.8%) | 10/44 (22.7%) | 0.009* |
| No vaginal dryness (CX24) | 63/165 (38.2%) | 63/156 (40.4%) | 74/141 (52.5%) | 0.012* |

[a] Wilcoxon signed-rank test (baseline vs. 12 months); Bonferroni-corrected threshold p < 0.017. * Significant after correction.
[b] Dyspareunia denominator = sexually active patients only (n = 44). QoL, quality of life; QLQ, quality-of-life questionnaire.

This divergence between improving global QoL and worsening sexual function is consistent with findings from other IGABT series (6,9,12,23).

## Discussion

This study adds exploratory outcome data to the literature on CT-guided IGABT survivorship across three domains. First, it provides prospectively collected vaginal morbidity and QoL data from one of the larger CT-guided IGABT cohorts published to date, contributing evidence for a setting that MRI-centred series cannot represent for the majority of global treatment centres (5,8). Second, it adds exploratory predictor data, identifying non-use of vaginal dilators and menopausal status as independently associated with grade ≥2 stenosis. Third, it characterises the dissociation between improving global QoL and declining sexual function over 12 months (12,13).

The oncologic outcomes — 98.9% LC at 1 year and dosimetric parameters within EMBRACE II benchmarks — suggest acceptable oncologic outcomes in an experienced CT-guided IGABT setting, consistent with published MRI-guided series (4,24,25). The prognostic importance of HR-CTV D90 $EQD_2$ (HR 0.94 per Gy, $p < 0.001$) is consistent with EMBRACE-I findings and supports target coverage adequacy as a central quality indicator (4,26,27).

The rate of grade 3 stenosis on clinical examination — observed in 48/165 evaluable patients (29.1%), corresponding to 48/155 patients with any stenosis (31.0%) — requires careful contextualisation. This reflects an anatomically defined endpoint (severe vault shortening and/or obliteration on direct examination), which is conceptually and numerically distinct from composite CTCAE grade ≥3 toxicity (9/165, 5.5%). The disparity arises because CTCAE-composite grading aggregates heterogeneous endpoints, some with low base rates, while clinical stenosis grading targets a single, high-prevalence structural outcome. Both metrics are reported in *Table 1* with explicit definitions. The high stenosis rate likely reflects in part the high baseline rate of tumour vaginal involvement (86.1%) in this advanced-stage cohort (6,10, 28,29). A descriptive surrogate analysis (*Table S1*) suggests that upper vaginal third involvement and postmenopausal status are more prevalent in patients developing grade 3 stenosis, consistent with known biological plausibility.

The exploratory logistic regression adds predictor data from a CT-guided cohort of this size. Non-use of vaginal dilators (OR 3.1, $p = 0.004$) was the strongest modifiable risk factor, consistent with the EMBRACE-I dilator study (9) and Cochrane evidence (14). Menopausal status (OR 2.4, $p = 0.027$) reflects atrophic changes compounding treatment-induced mucosal injury (15,28,30). These findings support prospective hypothesis-testing in larger cohorts and integration of structured rehabilitation into clinical pathways.

The QoL trajectory — global improvement alongside progressive sexual function decline — reflects a pattern increasingly recognised in cervical cancer survivorship literature (12,13,20,23). This dissociation argues against using global QoL as the sole survivorship metric.

### *Limitations*

This study has several limitations. The single-institution design limits generalisability. The exploratory logistic regression (EPV ≈ 20) is insufficient for definitive predictor estimation and requires external validation; the number of events per variable in Cox analyses (approximately 8-12) supports exploratory inference only. The proportional hazards assumption was assessed graphically using log-log survival plots, but formal residual-based testing was not performed; therefore, minor violations cannot be excluded. Missing QoL data were handled by LOCF in sensitivity analyses only; no formal pattern-mixture analysis for informative dropout was performed. Fifteen patients were censored before the 12-month assessment (10 recurrences, 5 deaths); this may underestimate late toxicity burden in the evaluable cohort. Vaginal dose metrics are unavailable due to CT contouring limitations when tumour involves the upper vaginal third (5); a descriptive surrogate analysis is presented in *Table S1*. Median follow-up (24.6 months) may be insufficient to capture the full late-toxicity trajectory. Dilator counselling was not delivered according to a formal written protocol, and compliance was self-reported, introducing recall and social desirability bias. Four patients with para-aortic nodal disease, reclassified from FIGO IVB to IIIC2 per FIGO 2018 (16), were included; their small number precludes subgroup analysis.

## Conclusions

In this descriptive, retrospective cohort of 180 LACC patients treated with CT-guided hybrid brachytherapy, overall composite CTCAE grade ≥ 3 vaginal toxicity occurred in 9/165 evaluable patients (5.5%) at 12 months. This finding must be interpreted alongside — not instead of — the anatomically graded stenosis rate: 155/165 evaluable patients (93.9%) had any degree of

vaginal stenosis, and grade 3 stenosis was observed in 48/165 evaluable patients (29.1%), corresponding to 48/155 patients with any stenosis (31.0%). A 29.1% rate of grade 3 clinical stenosis among all evaluable patients is not compatible with characterising vaginal toxicity as "low" without explicit disambiguation of these two distinct metrics; both must be communicated transparently to patients and reported clearly in future publications.

Global QoL improved over 12 months while sexual function declined progressively. This dissociation identifies a survivorship gap that is inadequately captured by composite QoL metrics alone. Non-use of vaginal dilators was the strongest independently modifiable predictor of grade $\geq 2$ stenosis in exploratory analysis. These findings support systematic consideration of structured vaginal rehabilitation from treatment completion, combined with targeted survivorship counselling for postmenopausal patients, as part of post-IGABT follow-up care.

This study provides retrospective real-world outcome data from a CT-guided IGABT setting that represents the dominant global practice environment. All findings are exploratory and require prospective validation in larger, multi-centre cohorts.

### *Authors' Contributions*

Conceptualization, B.A. and A.D.S.; methodology, E.M.; formal analysis, B-V.I.; investigation, B.A. and E.M.; data curation, V.S., A.D.S.; writing — original draft preparation, B.A.; writing — review and editing, B.A., E.M., A.D.S. and V.S.; supervision, A.D.S. All authors have read and agreed to the published version of the manuscript.

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### *Conflicts of Interest*

The authors declare no conflicts of interest.

### *Funding*

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### *Institutional Review Board Statement*

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Sanador Clinical Hospital (protocol date: 27 March 2023). Patient data were collected prospectively during clinical care; the retrospective analysis of the database was approved prior to data analysis. All data were anonymised prior to analysis.

### *Informed Consent Statement*

Written informed consent was obtained from all subjects involved in the study prior to enrolment. Consent included approval for retrospective data collection and publication of anonymised clinical outcomes.

### *Data Availability Statement*

The data supporting the findings of this study are available on request from the corresponding author. Data are not publicly deposited due to institutional privacy constraints.

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# Supplementary Material

**Table S1.** Descriptive comparison of available surrogate tumour and treatment variables by grade 3 vaginal stenosis status at 12 months (exploratory; not powered for hypothesis testing).

| Variable | Grade 3 Stenosis (n = 48) | No Grade 3 Stenosis (n = 107) | p-value (descriptive) |
|---|---|---|---|
| Upper vaginal third involvement — n (%) | 46/48 (95.8%) | 87/107 (81.3%) | 0.021 |
| Tumour size ≥ 50 mm — n (%) | 33/48 (68.8%) | 57/107 (53.3%) | 0.074 |
| FIGO stage IIIC–IVA — n (%) | 36/48 (75.0%) | 74/107 (69.2%) | 0.462 |
| HR-CTV D90 $EQD_2$, Gy — mean ± SD | 85.4 ± 6.2 | 84.9 ± 5.8 | 0.641 |
| IC/IS hybrid applicator — n (%) | 28/48 (58.3%) | 51/107 (47.7%) | 0.226 |
| Brachytherapy fractions — median (range) | 4 (4–5) | 4 (4–5) | 0.883 |
| Postmenopausal — n (%) | 33/48 (68.8%) | 52/107 (48.6%) | 0.022 |
| No vaginal dilator use — n (%) | 38/48 (79.2%) | 67/107 (62.6%) | 0.044 |

Denominators reflect evaluable patients at 12 months with any stenosis (n = 155; grade 3: n = 48, grade 1–2: n = 107). p-values are descriptive (chi-square or Mann–Whitney U): not powered for confirmatory inference. HR-CTV: high-risk clinical target volume; $EQD_2$: equivalent dose in 2 Gy fractions; IC: intracavitary; IS: interstitial; SD: standard deviation.