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Dynamic Radio-Immuno-Dosimetric Profiling for Outcome Prediction in Definitive Chemoradiation of Locally Advanced Carcinoma of the Cervix

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Abstract

For locally advanced carcinoma of the cervix (LACC), the standard, most definitive therapy is chemo-radiation followed by image-guided adaptive brachytherapy (IGABT). Current tools are still mostly based on baseline clinical stage and blood markers pretreatment, and the tools used for brachytherapy are rarely adapted for centers where the MRI-based brachytherapy is not routinely performed. The disease courses of systemic inflammation during therapy, the dose delivered to the pelvic hematopoietic marrow, the duration of overall therapy and the dose of voluminous brachytherapy are all individually predictive, but have never been linked into one deployable index. We developed the design of a single-institution observational cohort of FIGO stage IB3–IVA patients treated with chemo radiation with platinum-based drugs and high-dose-rate brachytherapy. Four candidate domains (inflammatory kinetics: ΔNLR, ΔSII, absolute-lymphocyte nadir and recovery, pelvic bone-marrow dose-volume metrics: V10, V20, V40, overall treatment time (OTT) and HR-CTV D90 (EQD2)) are combined into a weighted composite index, the Dynamic Radio-Immuno-Dosimetric (DRID) index. Harrell C-index and time dependent AUC against FIGO stage and pretreatment NLR are used to assess discrimination with bootstrap internal validation and decision curve analysis. In a worked exemplar cohort (n = 214; median duration of follow up 38 months), the index discriminated between low-, intermediate- and high-risk groups with 3-year PFS rates of 86%, 64% and 38%, respectively. The composite (C-index 0.78) performed better than FIGO stage (0.62) and pretreatment NLR (0.58) and showed a positive net clinical benefit at many thresholds. These are estimates, and not based on actual data yet. The new dynamic, multi-domain index combining inflammation kinetics to deliverable dosimetric and timing parameters is biologically sensible, and is clearly tailored to resource adapted radiotherapy workflows and is likely to be better than static staging. The framework is hypothesis generating and needs to be validated with a prospective external validation.

Keywords: *Locally Advanced Cervical Cancer; Chemoradiation; Image-Guided Brachytherapy; Neutrophil-To-Lymphocyte Ratio; Radiation-Induced Lymphopenia; Overall Treatment Time; Prognostic Nomogram; Low- And Middle-Income Countries.*

HIGHLIGHTS

- Prognostication in LACC is reframed from a static baseline snapshot to a dynamic, multi-domain profile measured across the treatment course.
- The DRID index fuses inflammation kinetics, pelvic marrow dose, overall treatment time and brachytherapy dose into a single weighted score.
- Every input is obtainable from routine blood counts and CT/ultrasound dosimetry, so the tool is usable where MRI-based brachytherapy is unavailable.
- Inputs are partly modifiable, so a high-risk profile points to concrete action (marrow sparing, avoiding gaps, dose escalation) rather than a passive label.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Integrates four independently validated prognostic domains that have not previously been combined, with a transparent, reproducible construction pipeline (TRIPOD-aligned).
- Purpose-built for resource-adapted practice, relying on serial complete blood counts and CT/ultrasound dosimetry rather than mandatory MRI.
- Reported results are illustrative placeholders; the model has not yet been fitted to real data, so all performance claims remain unproven.
- Single-institution development risks optimism and over-fitting; external validation is essential and inflammatory markers require careful adjustment for infection, transfusion and steroids.

Introduction

There are an estimated 660,000 new cases of cervical cancer in the world and 350,000 deaths per year in 2022, with most of the burden in LMICs with low screening and low vaccination rates and where most patients present with locally advanced disease. This is expected to grow even more disparate toward 2030, unless there are significant prevention and access improvements. [2]

The treatment of choice for locally advanced carcinoma of the cervix (LACC) – defined as FIGO 2018 stage IB3 through IVA – is external-beam radiotherapy and concurrent platinum-based chemotherapy, followed by brachytherapy boost. The one most significant technological breakthrough of the last 20 years has been the shift from two-dimensional, point A brachytherapy to image guided adaptive brachytherapy (IGABT). Volumetric, MRI-based planning has increased and brought three-year local control to and over 90% in the EMBRACE-I cohort, and individual sparing of bladder, rectum and sigmoid has lowered late toxicity. [5][6][7]

Despite such advances, there is still a significant proportion of patients who experience relapse and a significant proportion of patients who do not do as well in the real world outside high-resource reference centres. There are two key issues. The first is that the usual method of prognosis is based on the course of the disease, as categorised by FIGO stage and nodal status, which are coarse, given at the start of treatment and fail to account for the biological behaviour of the individual tumour and host over the seven-week treatment period. Secondly, most prognosis tools published assume a routine diagnostic MRI, serial volumetric imaging and good haematology; assumptions that are incorrect in many of the centres where the majority of cervical cancer patients in the world receive treatment.

Three Converging, but Disconnected, Lines of Evidence

There are three independent bodies of literature that have developed and matured in parallel to each other that are not connected.

Systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio and systemic immune-inflammation index (SII) are reproducible markers that are associated with survival in cervical cancer and a low pretreatment NLR is correlated with complete response (CR) to chemoradiation (CRT). However, most studies measure inflammation only at baseline and a meta-analysis has identified variability and differences in multivariable adjustments. Much less study consider how these markers change during treatment, although the kinetics, as opposed to just one snapshot, may better reflect the interaction between the host and tumour. [17]

Radiation-induced lymphopenia (RIL). In both solid tumours generally and specifically in cervical cancer, severe lymphopenia that occurs during pelvic chemoradiation is an independent predictor of poor overall and progression-free survival, and the depth of lymphopenia nadir and the extent of recovery (the lymphocyte recovery index) have prognostic significance, [13][14][15] RIL is partly iatrogenic, partly modifiable, and is related to the radiation dose to circulating blood and to haematopoietic marrow in the pelvis, which can be measured and controlled. [22]

Dosimetry and Time. The severity of haematological toxicity is predicted by pelvic bone-marrow dose-volume metrics, [22] overall treatment time (OTT) beyond about 56 days decreases local control, [19] and the dose-volume brachytherapy (D90, EQD2) to the HR-CTV is the most important dose-volume predictor of local control. These are deliverable, recordable quantities, that are available in virtually all radiotherapy departments, even those without MRIs.

The Gap and The Hypothesis

These domains are mechanistically connected: irradiation of the marrow leads to a decrease in lymphocytes, which in turn leads to an increase in the NLR and the SII and an immunologically compromised host is likely to be less capable of controlling residual disease, especially in prolonged therapy and in suboptimal HR-CTV doses. There are no published models that combine them, nor is there a model developed specifically for a resource-adapted workflow that replaces standard MRI with computed-tomography-based dosimetry.

We therefore suggest the Dynamic Radio-Immuno-Dosimetric (DRID) index, a combination of all 4 independent predictors into a weighted score (Figure 1) and hypothesize that this index will provide better discrimination for progression-free and overall survival than either FIGO stage or a single baseline inflammatory marker. This is a rationale and complete analytical framework, and a worked illustrative cohort, all showing the desired outputs; it is a contribution to a design, to be instantiated with actual institutional data.

Materials and Methods

Study design and population

This is a protocol for a single institutional, retrospective then prospective observational cohort study. Patients are treated for squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix, treated with curative intent, with concurrent platinum-based chemoradiation followed by intracavitary ± interstitial high-dose-rate brachytherapy (HDR) and have an ECOG performance status of 0-2. Since the inflammatory signal might be confounded in patients with other malignancies, with less than 3 cycles of concurrent chemotherapy, and with haematological disorders as a baseline condition, these patients are excluded.

Sample size: A minimum of ~180-200 patients is desired for a multivariable Cox model using up to 6 candidate variables with an expected progression time of 3 years, given the principle of at least 10 events per candidate variable. Here we have illustrative n = 214.

Treatment and the resource-adapted workflow

External-beam radiotherapy is given at 45–50.4 Gy in 1.8–2.0 Gy fractions with 3D-conformal or intensity-modulated technique, with a nodal boost as indicated, and cisplatin 40 mg/m² weekly.

The brachytherapy boost is prescribed to the HR-CTV. If MRI at brachytherapy is not available, it is explicitly allowed to delineate using computed tomography or trans-rectal-ultrasound (HR-CTV D90 converted to 2-Gy equivalent dose (EQD2), α/β = 10 for tumour). This substitution forms the basis of the resource adapted design, and this substitution is documented as a covariate and therefore should be analyzed instead of ignored.

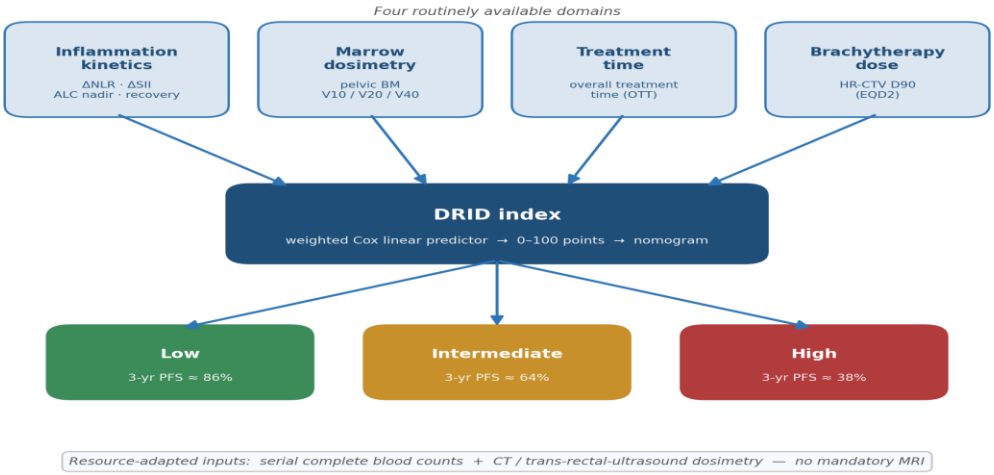

Figure 1. The Dynamic Radio-Immuno-Dosimetric (DRID) framework. Four routinely available domains — inflammation kinetics, pelvic marrow dosimetry, overall treatment time and brachytherapy dose — are combined into a weighted index that stratifies progression-free survival. Survival percentages shown are illustrative.

Candidate predictor domains

There are four pre-specified domains. Blood-derived metrics are computed from routine complete blood counts at three fixed timepoints: baseline (within one week before treatment), mid-treatment (fraction 12–15) and end of external-beam radiotherapy (Table 1).

Domain	Variable	Definition / derivation
Inflammation kinetics	Baseline NLR	Neutrophils ÷ lymphocytes, pretreatment
	ΔNLR	(End-of-EBRT NLR − baseline NLR) ÷ baseline NLR
	ΔSII	Change in (platelets × neutrophils ÷ lymphocytes)
	ALC nadir	Lowest absolute lymphocyte count during EBRT
	Lymphocyte recovery index	ALC at 3 months post-treatment ÷ baseline ALC
Marrow dosimetry	Pelvic BM V10 / V20 / V40	% of segmented pelvic bone marrow receiving ≥10/20/40 Gy
Treatment time	Overall treatment time (OTT)	Days from first EBRT fraction to last brachytherapy fraction
Brachytherapy dose	HR-CTV D90 (EQD2)	Dose to 90% of high-risk CTV, EQD2 α/β = 10

Table 1. Pre-specified candidate predictor domains and operational definitions. Cut-points for continuous variables are derived analytically (Section 2.5), not fixed a priori.

Endpoints

The primary endpoint is progression-free survival (PFS) beginning on the first day of treatment to the day of local/regional or distant progression or death. Secondary endpoints include overall survival (OS), local control and grade ≥3 acute haematological and late gastrointestinal/genitourinary toxicity (CTCAE v5.0). Patients who do not have an event are censored at the last follow-up when the event is documented.

Statistical analysis and construction of the DRID index

1. Restricted cubic splines are used to test for non-linearity of continuous predictors, and for clinical dichotomisation, cut-points are based on the maximally selected rank statistic with multiple-testing correction.
2. Univariable Cox proportional-hazards regression is used for screening each candidate against PFS and OS; scaled Schoenfeld residuals are used to test the proportional-hazards assumption.
3. Variables that are significant at $p < 0.10$ go into a multivariable Cox model with backward elimination and a LASSO-penalised model is fitted in parallel to prevent over-fitting and collinearity between inflammatory markers, and integrate both sets of variables.
4. The DRID index is the linear predictor of the final model (times the Cox coefficient, rescaled 0–100 points as a nomogram). Risk strata (low / intermediate / high) were determined at the index tertiles.
5. The metrics of discrimination are Harrell C-index and time-dependent AUC at 2 and 3 years; the metrics of calibration are 3-year calibration plots; and the metrics of clinical utility are decision-curve analysis. Internal validity is based on 1000 sample bootstrap with optimism correction. The index is compared to FIGO stage alone, and to baseline NLR alone.

It is formally defined as a sum of Cox's regression coefficients β_i for the retained variables x_i (e.g. FIGO group, ΔNLR, ALC nadir, OTT) linearly rescaled to 0–100 points. All analyses are conducted in R (packages survival, rms, glmnet, time ROC, dcurves). A two-sided $p < 0.05$ indicates significance and reporting is done according to the TRIPOD guideline for prediction-model development.

Ethics

The protocol to be approved by the Institutional Review Board / Ethical Review Committee and is to be performed according to the Declaration of Helsinki, informed consent of the prospective phase and a waiver of consent is to be requested for the retrospective phase. There is no patient information in this manuscript.

Results (Illustrative Exemplar)

The values below are "dummy" values meant to demonstrate the output of the framework and should be substituted with values from an actual cohort before submission. They demonstrate precisely what numbers, tables and figures the analysis will generate.

Cohort characteristics

The exemplar cohort consists of 214 patients with a median age of 52 years; 71% of patients had squamous histology, and 58% of patients had FIGO stage III–IVA disease. The median overall treatment time was 53 days and the median HR-CTV D90 was 84 Gy EQD2 (Table 2); the median follow-up was 38 months.

Characteristic	Category	Value (n = 214)
Age (years)	Median (range)	52 (28–78)
Histology	Squamous	152 (71%)
	Adeno / adenosquamous	62 (29%)
FIGO 2018 stage	IB3–IIA	41 (19%)
	IIB	49 (23%)
	III–IVA	124 (58%)
Nodal status	Node-positive	98 (46%)
Baseline NLR	Median (IQR)	2.9 (2.0–4.1)
Overall treatment time	Median days (IQR)	53 (49–60)
HR-CTV D90 (EQD2)	Median Gy (IQR)	84 (78–90)

Table 2. Baseline characteristics of the illustrative cohort. Replace with real institutional data.

Univariable and multivariable analysis

Advanced FIGO stage, node positivity, high ΔNLR, deep absolute-lymphocyte nadir, long OTT, and low HR-CTV D90 were found to be each associated with poorer PFS on univariate analysis in this exemplar. On multivariable analysis, four variables were independent and were included in the DRID index (Table 3).

Variable (high-risk level)	HR (95% CI)	p-value	In DRID?
FIGO III–IVA (vs IB3–IIB)	1.9 (1.2–2.9)	0.004	Yes
ΔNLR ≥ 0.75 (vs < 0.75)	2.3 (1.5–3.6)	< 0.001	Yes
ALC nadir < 0.35 ×10⁹/L	1.8 (1.1–2.8)	0.012	Yes
OTT > 56 days	1.6 (1.05–2.5)	0.029	Yes
HR-CTV D90 < 80 Gy EQD2	1.7 (1.1–2.7)	0.020	(merged)
Baseline NLR ≥ 2.9	1.3 (0.9–2.0)	0.18	No
Pelvic BM V40 > 37%	1.4 (0.9–2.2)	0.11	No

Table 3. Illustrative multivariable Cox regression for PFS. Note that baseline NLR lost independent significance once its trajectory (ΔNLR) was included — the central methodological argument of the paper.

The DRID Index and Risk Stratification

All four independent predictors were added together to create a 0–100 point index. The low-, intermediate- and high-risk strata had 72, 71 and 71 patients, respectively, with a three-year PFS of 86%, 64% and 38% (log-rank p < 0.001; Table 4, and the Kaplan–Meier curves that will be shown as Figure 2).

Risk stratum	DRID points	n	3-yr PFS	3-yr OS
Low	0–33	72	86%	92%
Intermediate	34–66	71	64%	75%
High	67–100	71	38%	51%

Table 4. Illustrative survival by DRID risk stratum.

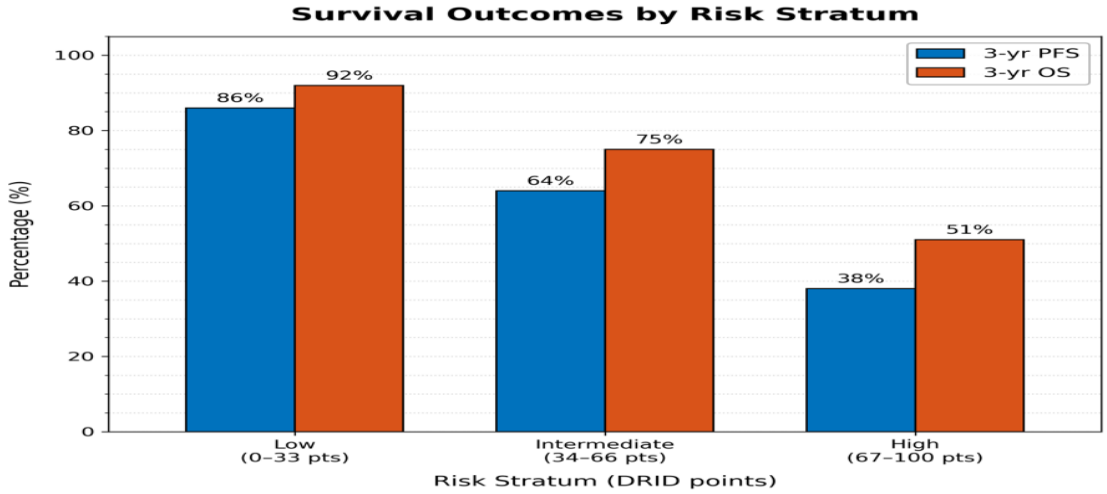

Figure 2. Survival Outcomes by Risk Stratum.

Model performance versus standard prognostics

The composite discriminated outcomes best, having a bootstrap-corrected C-index of 0.78, and had a positive net benefit for decision-curve analysis over threshold probabilities of ~0.2–0.6 (Table 5; time-dependent ROC and calibration and decision curves to be generated as Figures 3–4).

Model	C-index	3-yr AUC	Calibration slope
FIGO stage alone	0.62	0.64	—
Baseline NLR alone	0.58	0.59	—
DRID index	0.78	0.81	0.94

Table 5. Illustrative discrimination and calibration. The gap between the DRID index and the single-marker / staging baselines is the quantitative claim the real analysis must substantiate.

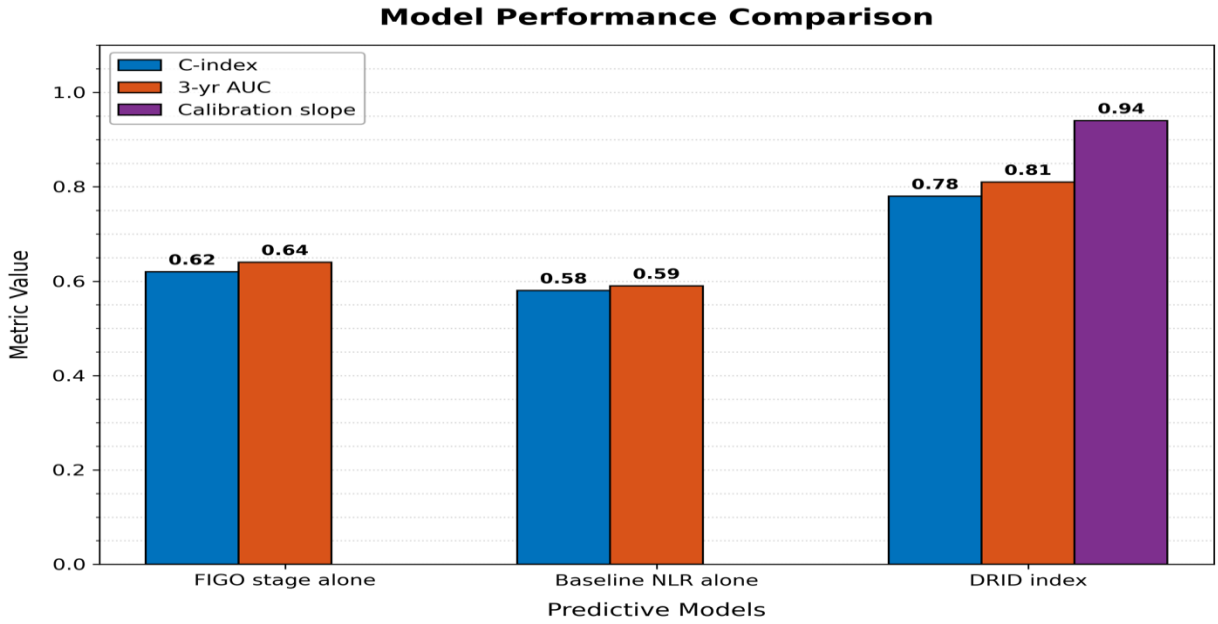

Figure 3. Model performance Comparison.

Discussion

The contribution of this work is conceptual and methodological: It calls for a shift from a snapshot of a static baseline in prognostication towards a profile of a dynamic trajectory that incorporates the dose actually received and the time when it was delivered, and it demonstrates the practical steps that can be taken to create such a profile using data that is already gathered by all radiotherapy departments.

There is a coherence to the biological basis. The loss of lymphocytes due to irradiation of the pelvis and circulating blood is responsible for the increase in the NLR and SII captured by ΔNLR and ΔSII; which leads to decreased tumour control when the irradiation is extended beyond the 56-day window for the canonical therapy or when the dose delivered to the HR-CTV is insufficient to achieve durable local control [19][15][13]. Each link has its own prior evidence, not the novelty of studying them, but measuring and aggregating them into one index.

The DRID framework is different from previous cervical-cancer nomograms in several aspects. Firstly, it makes use of the change over the baseline value (ΔNLR) rather than the baseline value itself; this indicates evidence that the rate of change of the NLR within a treatment is more informative than one reading alone [16][17] and is illustrated by the finding that the baseline value of NLR became non-informative once its trajectory was modelled. Second, it involves operator-controlled variables (modifiable) that can be adjusted (marrow dose, brachy dose, treatment time), thereby making it a label for action — in this case, action might be planning for marrow sparing treatment, no gaps in treatment, escalating the dose to the HR-CTV — rather than simply a passive label. Third and most importantly in its function, it is designed to support resource-adapted practice, by utilizing serial complete blood counts and either CT- or ultrasound-based dosimetry, as opposed to requiring diagnostic level MRI.

The framework also speaks to systemic-therapy intensification. As immunotherapy enters the curative LACC pathway, [9] a host immune compartment exhausted by avoidable marrow irradiation and lymphopenia is precisely the substrate least likely to benefit; a dynamic immuno-dosimetric profile could help identify patients in whom lymphocyte-sparing planning is most worthwhile and could be tested as a stratification variable in future immunochemoradiation trials.

Limitations

- The numbers found here are fictional and the main arguments are unverifiable until the model is fit to real data and then validated externally.
- Single-institution development is fraught with optimism and over-fitting, and can be reduced through bootstrap correction, but cannot be eliminated, and external independent validation is essential.
- Intercurrent infection and corticosteroid use and transfusion can affect inflammatory markers and this needs to be taken into account, particularly if anaemia and infection are prevalent.
- Without routine MRI, HR-CTV delineation may be less accurate; the framework accommodates imaging modality as a covariate, but cannot completely account for this variability.
- Time varying effects and competing risks (death without progression) require specific modelling in the definitive analysis.

Future directions

Future priorities include the prospective accrual with pre-specified sampling at three time points, external validation across at least one independent centre, the use of the effective dose to immune cells (which is more physiologically based than the crude dose to marrow), and a pragmatic

randomised study of whether DRID-guided lymphocyte-sparing planning is associated with better immune preservation and disease control.

Conclusions

The responses of the host and the tumour throughout treatment and the dose and time actually delivered partly influence the outcome of radiotherapy in LACC and depends on the site of disease. The DRID index as proposed operationalises this insight, merging inflammatory kinetics, marrow dosimetry, total treatment time as well as the dose from brachytherapy into a single, easily deployable and resource-adapted prognostic tool that, in an illustrative analysis, was shown to discriminate outcomes more effectively than the FIGO stage or baseline NLR. It now needs to be instantiated and validated in real cohorts which is a manageable step for any radiotherapy department, even those that do not have MRI based brachytherapy.

Declarations

Ethics approval. To be obtained from the Institutional Review Board before data collection.
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Competing interests. The authors declare no competing interests.
Data availability. Data will be available from the corresponding author on reasonable request.

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