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Evaluation of an Early Regression Index (ERI_{TCP}) as Predictor of Pathological Complete Response in Cervical Cancer: A Pilot-Study

Davide Cusumano [1], Francesco Catucci [1], Angela Romano [1], Luca Boldrini [1,*], Antonio Piras [2], Sara Broggi [3], Claudio Votta [1], Lorenzo Placidi [1], Matteo Nardini [1], Giuditta Chiloiro [1], Alessia Nardangeli [1], Viola De Luca [1], Bruno Fionda [1], Maura Campitelli [1], Rosa Autorino [1], Maria Antonietta Gambacorta [1], Luca Indovina [1], Claudio Fiorino [3] and Vincenzo Valentini [1]

[1] Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, 00168 Rome, Italy; davide.cusumano@policlinicogemelli.it (D.C.); catuccifr@gmail.com (F.C.); angelaromano89@gmail.com (A.R.); claudio.vt@hotmail.it (C.V.); lorenzo.placidi@policlinicogemelli.it (L.P.); matteo.nardini@unicatt.it (M.N.); giuditta.chiloiro@policlinicogemelli.it (G.C.); alessia.nardangeli@policlinicogemelli.it (A.N.); viola.deluca89@gmail.com (V.D.L.); bruno.fionda@policlinicogemelli.it (B.F.); maura.campitelli@policlinicogemelli.it (M.C.); rosa.autorino@policlinicogemelli.it (R.A.); mariaantonietta.gambacorta@policlinicogemelli.it (M.A.G.); luca.indovina@policlinicogemelli.it (L.I.); vincenzo.valentini@policlinicogemelli.it (V.V.)

[2] UO Radioterapia Oncologica, Villa Santa Teresa, 90011 Bagheria, Palermo, Italy; antoniopiras88@gmail.com

[3] Medical Physics, San Raffaele Scientific Institute, 20132 Milano, Italy; broggi.sara@hsr.it (S.B.); fiorino.claudio@hsr.it (C.F.)

* Correspondence: luca.boldrini@policlinicogemelli.it; Tel.: +39-06-3015-5339

Received: 6 October 2020; Accepted: 6 November 2020; Published: 11 November 2020

Featured Application: The paper aim to propose an image-based parameter for response prediction in cervical cancer.

Abstract: Background: Recent studies have highlighted the potentialities of a radiobiological parameter, the early regression index (ERI_{TCP}), in the treatment response prediction for rectal cancer patients treated with chemoradiotherapy followed by surgery. The aim of this study is to evaluate the performance of this parameter in predicting pathological complete response (pCR) in the context of low field MR guided radiotherapy (MRgRT) for cervical cancer (CC). Methods: A total of 16 patients affected by CC were enrolled. All patients underwent a MRgRT treatment, with prescription of 50.6 Gy in 22 fractions. A daily MR acquisition was performed at simulation and on each treatment fraction. Gross tumor volume (GTV) was delineated on the MR images acquired at the following biological effective dose (BED) levels: 14, 28, 42, 54 and 62 Gy. The ERI_{TCP} was calculated at the different BED levels and its predictive performance was quantified in terms of receiver operating characteristic (ROC) curve. Results: pCR was observed in 11/16 cases. The highest discriminative power of ERI_{TCP} was reported when a BED value of 28 Gy is reached, obtaining an area under curve (AUC) of 0.84. Conclusion: This study confirmed ERI_{TCP} as a promising response biomarker also for CC, although further studies with larger cohort of patients are recommended.

Keywords: MR-guided radiotherapy; predictive models; cervical cancer

1. Introduction

Cervical cancer (CC) represents one of the most common and severe female cancers. More than 500,000 new cases per year are diagnosed in the world and despite the significant therapeutic

improvements achieved in the recent years, the number of deaths per year ranges from 250,000 to 350,000 [1–3]. The clinical management of CC involves different specialists, with the aim of tailoring the treatment on the basis of the tumor staging [4].

According to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification, stage IB2-IVA patients are considered as locally advanced cervical cancer (LACC). The standard of care for these patients is represented by neoadjuvant chemoradiotherapy (nCRT) followed by brachytherapy boost, with the primary aim of organ preservation [5].

Despite the good results in terms of overall survival and local control achieved through this approach, alternative approaches have been investigated in the scientific community to further reduce the rate of treatment failure [6,7].

In this context, some experiences have reported the advantage to administer neo-adjuvant external beam radiotherapy with concomitant chemotherapy followed by radical surgery, aiming to remove the residual tumor foci resistant to the previous treatment and reporting favorable rates of local control and disease-free survival, with acceptable acute and long-term toxicity profiles [8–10].

The response to nCRT followed by surgery is quantified on the basis of the histological evaluation of the surgical specimen: Pathological complete response (pCR) is achieved when no residual tumor foci are present.

Clinical experiences reported pCR rates of about 50% for LACC patients undergoing nCRT, also observing that the pCR status is associated with higher rates of long-term and disease-free survival [11–14].

Regardless of the clinical approach adopted, there is growing interest towards the identification of treatment response predictors, to move towards a more personalized clinical approach, avoiding unnecessary surgical procedures in patients with high probability of pCR or modifying the clinical management in the case of poor responders.

Different models have been proposed in literature to predict treatment response in CC, some of them including only clinical data, others combining also image parameters extracted from magnetic resonance (MR) or computed tomography (CT) images acquired at disease staging [15–18].

Magnetic resonance imaging (MRI) is considered the elective imaging modality for diagnosis and staging of CC and the recent development of hybrid MRI-radiotherapy systems, combining a linear accelerator with an on-board MR scanner, may represent a significant step-forward in the clinical management of this disease, as demonstrated by some preliminary experiences [19–21].

The availability of daily MR images leads to the possibility to define image-based predictive models able to study the patient treatment sensitivity by means of the analysis of the MR images acquired during the course of treatment.

In this context, a radiobiological parameter able to predict the treatment response in the locally advanced rectal cancer has been recently proposed and validated, modelling the tumor shrinkage during the first weeks of nCRT treatment through a statistical approach. This parameter, known as early regression index (ERI_{TCP}), combining the tumor volume measured on the MR images acquired at simulation and at mid-therapy, is able to identify the patients who will have complete response with high AUC value on low and high field MR images [22,23].

Aim of this hypothesis generating study is to evaluate the applicability of this parameter in the context of response of nCRT in CC, quantifying its performance in predicting pCR by using MR images acquired using a low field MR-guided radiotherapy unit [24].

2. Materials and Methods

2.1. Patients Selection Criteria and Treatment Workflow

Patients affected by LACC (FIGO IB2-IVA) were enrolled in this study, with the following inclusion criteria: Patients affected by biopsy proven LACC with no evidence of distant metastases at the

radiological staging exams; Eastern Cooperative Oncology Group (ECOG) performance status ≤2, no pregnancy or breastfeeding at the moment of nCRT and at least 18 years old at the time of diagnosis.

Informed consent for therapy and image analysis purposes was acquired from all patients. Patients presenting clinical contraindications to MRI (e.g., presence of non MRI-compatible implanted devices, claustrophobia or major psychiatric disorders) or denying specific consent to MR guided radiotherapy (MRgRT) were not included.

The diagnostic workflow consisted in a gynecological exam, a diagnostic 1.5 T MR of the abdominal-pelvic site and a whole-body ^{18}FDG-positron emission tomography (PET)-CT staging scan.

All the patients underwent nCRT, combining weekly 40 mg/m^2 of cisplatin with concurrent MRgRT, administered using a simultaneous integrated boost (SIB) technique delivered in 22 fractions and prescribing a dose value of 50.6 Gy (2.3 Gy/fraction) to clinical target volume (CTV)1 and 39.6 Gy (1.8 Gy/fraction) to CTV2 [20].

All the patients signed a specific informed consent describing in detail the chosen therapeutic approach.

Radiotherapy was delivered using a 0.35 T MRgRT hybrid unit (ViewRay Inc., Mountain View, CA, USA) and therapy volumes were delineated on the 0.35 T TRUFI MR scan acquired during treatment simulation and using co-registered diagnostic 1.5 T staging MR and ^{18}FDG PET-CT images as supporting imaging.

The Gross Tumor Volume (GTV) was identified using the MR and PET-CT supporting images. CTV1 coincided to GTV and CTV2 was delineated as the union of the entire cervix, the uterus, parametria, vagina (entire or upper half, according to presence or absence of disease) and the corresponding drainage nodal.

If the pelvic nodes resulted positive at staging imaging, the common iliac nodes were included in the CTV2 volume, while the para-aortic nodes were included in case that the common nodes were positive [20]. CTV1 and CTV2 were expanded with 5 mm isotropic margin to generate the corresponding planning target volumes, following the institutional MRgRT guidelines [21].

An online adaptive procedure was administered in the treatment fractions where the positioning MR image showed that the GTV was not included in the Planning Target Volume (PTV) margins. GTV, PTV, bladder, bowel bag and rectum were re-contoured in case of online adaptive.

From six to eight weeks after the end of the treatment a restaging was performed, through a gynecological visit and a new MRI and ^{18}FDG PET-CT acquisition. A Querleu–Morrow radical hysterectomy with pelvic lymphadenectomy was performed for each patient within 8 weeks of the end of nCRT [8].

Pathological response to treatment was evaluated on surgical specimens, and three categories of treatment response were identified:

- ✓ Complete response (pR0), as absence of any residual tumor cells at any site;
- ✓ Microscopic response (pR1), as presence of persistent tumor foci not exceeding 3 mm for the maximum dimension;
- ✓ Macroscopic response (pR2), as presence of persistent tumor foci exceeding 3 mm for the maximum dimension

pCR was considered in case of pR0 [25].

2.2. MRI Imaging Protocol and ERI_{TCP} Definition

A total of 16 patients were enrolled: All of them underwent a MRI protocol consisting of the acquisition of a T2/T1-weighted MR image each day of therapy (including simulation), acquired using a true fast imaging with steady state precession (TrueFISP) sequence [26].

Images were acquired using the 0.35 T on-board MR scanner integrated into the MRIdian system (ViewRay Inc, Mountain View, CA, USA), with a spatial resolution of 1.5 mm^3 and acquisition time of 175 s.

For the purposes of this study, the GTV was retrospectively delineated by two radiation oncologists with gynecological cancer expertise, blinded with respect the outcome of therapy.

Figure 1 shows a MR image sample with the tumor delineated at the simulation and at 10th day of therapy.

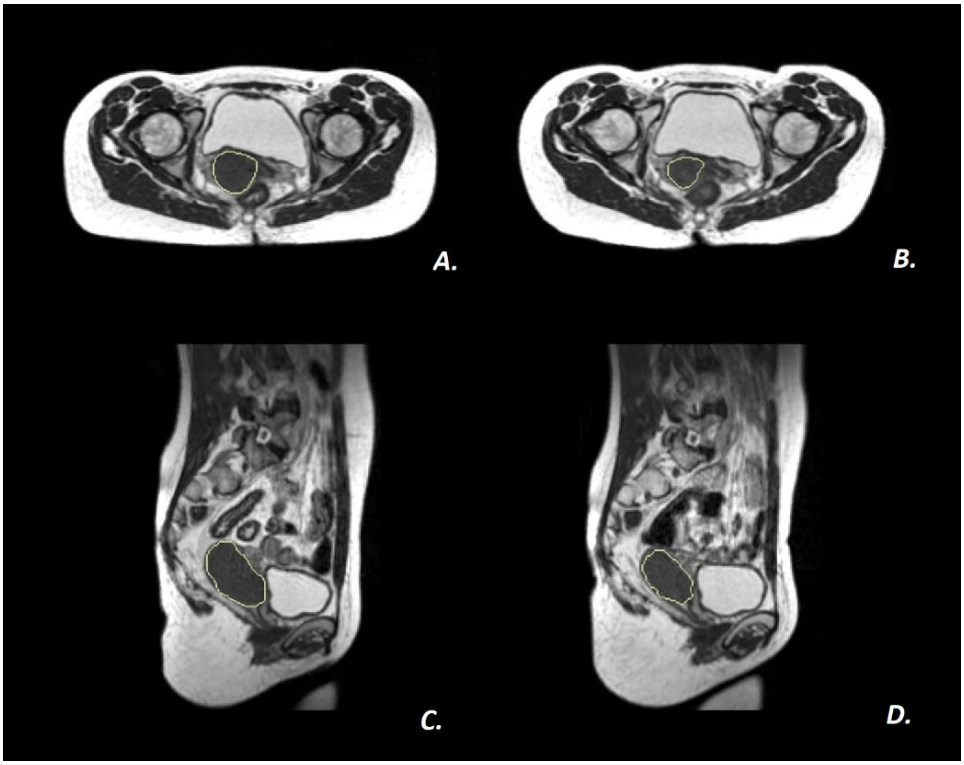

Figure 1. Gross tumor volume (GTV) delineated on simulation imaging and at fraction 10 in axial (**A**) and (**B**) and sagittal plan (**C**) and (**D**).

2.3. ERI_{TCP} Definition and Performance Evaluation

According to the original definition, the early regression index was calculated as follows [23]:

$$ERI_{TCP} = -ln\left[\left(1 - \left(\frac{V_{ther}}{V_{pre}}\right)\right)^{V_{pre}}\right]$$

where V_{pre} is the GTV volume calculated on the MR image acquired during simulation and V_{ther} represents the volume measured on the MR images acquired during the MRgRT treatment.

To identify the optimal time for pCR prediction, GTVs were delineated on MR images acquired at different fractions, and the ERI_{TCP} was calculated at different dose levels. The physical dose values were converted in biologically effective doses (*BED*) to make generalizable the results, using the following formula:

$$BED = nd\left(1 + \frac{d}{\frac{\alpha}{\beta}}\right)$$

where d is the dose per fraction, n is the number of fractions and α/β is the ratio representative of the tumor radio sensitivity, set equal to 10 Gy [27].

ERI_{TCP} was then calculated at the following BED values: 14, 28, 42, 54 and 62 Gy.

The ERI_{TCP} performance in identifying pCR patients was evaluated calculating the area under curve (AUC) under the receiver operating characteristic (ROC) curve for each dose level, estimating also the 95% exact binomial confidence interval according to the Clopper–Pearson method [28].

For each ERI index calculated, the Youden index (J) was also calculated at different threshold levels, and the one maximizing J was considered as best cut-off level.

The performance of the different ERI_{TCP} indices at the best cut-off level was then quantified considering specificity and sensitivity. The same analysis in terms of ROC curve was performed for the tumor volume calculated at simulation.

The BED value where the ERI_{TCP} reported the higher AUC value was identified as the optimal BED level to predict pCR. The ROC curves calculated at different BED values were then compared using the DeLong's test for correlated ROC curves [29].

Lastly, the robustness of ERI_{TCP} against inter-observer variability in tumor delineation was tested, comparing the volume of the contours independently delineated by the two radiation oncologists using the Mann–Whitney test for paired samples and the intra-class correlation index (ICC) [30,31]. The whole statistical analysis was performed using various software packages implemented in R environment [32,33].

3. Results

The clinical characteristics of the patients enrolled in this study at diagnosis and after surgery are reported in Table 1.

Table 1. Clinical information of the patients enrolled in the study.

Clinical Characteristics	Cases (Percentage)
Histology at the diagnosis	
■ Squamous cell carcinoma	15 (94%)
■ Clear cell adenosquamous carcinoma	1 (6%)
FIGO Stage at the diagnosis	
■ IIA	5 (31.3%)
■ IIB	10 (62.5%)
■ IIIC1	1 (6.2%)
Nodal status	
■ cN0	5 (31.3%)
■ cN1	11 (68.7%)
Pathological Response	
• pR0	11 (68.7%)
• pR1	3 (18.8%)
• pR2	2 (12.5%)

The median age of the patients at the diagnosis was 50.2 years (range 32–84 years), while pCR was achieved in 11/16 patients leading to a pCR rate of 68.7%. Table 2 summarizes the treatment fractions analyzed, with the corresponding physical and biological doses [34].

The median tumor volumes obtained by the two observers with the corresponding ranges and the results of the inter-observer analysis (*p*-value of Mann–Whitney test and ICC) are summarized in Table 3, to varying of the BED levels in Table 3.

High absolute agreement was observed in the GTV delineations performed by the two observers for all the different investigated time points, reporting no statistically significant differences in terms of Mann–Whitney test and high values in terms of ICC.

Table 2. Analyzed fractions and corresponding physical and biological biologically effective doses (BED) values, considering an α/β equal to 10 Gy for the tumor.

ERI	Fraction	Physical Dose	BED
$ERI_{14\ Gy}$	5	11.5 Gy	14.1 Gy
$ERI_{28\ Gy}$	10	23 Gy	28.3 Gy
$ERI_{42\ Gy}$	15	34.5 Gy	42.9 Gy
$ERI_{54\ Gy}$	19	43.7 Gy	53.8 Gy
$ERI_{62\ Gy}$	22	50.6 Gy	61.7 Gy

Table 3. Results of inter-observer variability to varying of the different BED levels.

BED	Median Tumor Volume (cc)		*p*-Value (Mann–Whitney)	ICC
	Observer 1	Observer 2		
0 Gy (Simulation)	50.5 (7.4–243.6)	45.9 (10.4–259.3)	0.13	0.99
14 Gy	33.7 (6.3–173.4)	33.1 (8.5–155.5)	0.57	0.98
28 Gy	25.8 (4.3–122.3)	21.5 (8.1–108.4)	0.18	0.98
42 Gy	22.2 (4.0–84.5)	20.0 (7.0–72.9)	0.23	0.96
54 Gy	14.7 (3.4–60.8)	33.1 (3.5–59.6.5)	0.53	0.95
62 Gy	11.6 (1.5–50.2)	13.0 (2.6–51.7)	0.32	0.97

The ERI_{TCP} was calculated at the different BED levels considering the contours of both observers and its ability in predicting treatment outcome was quantified by means of the ROC curves, as reported in Figure 2.

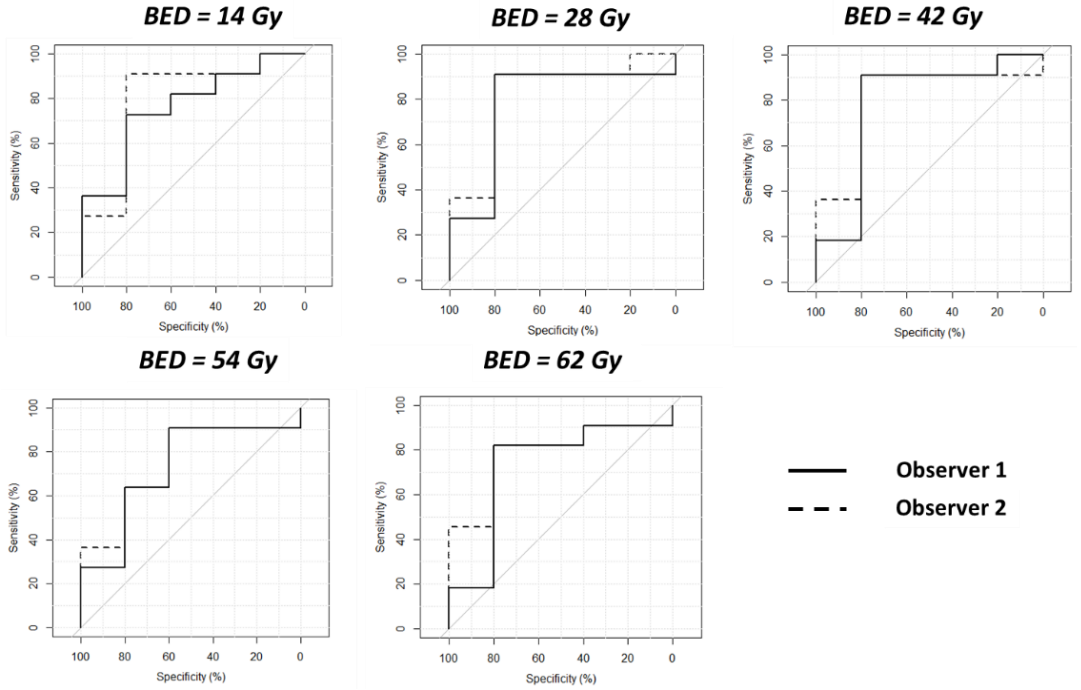

Figure 2. Receiver operating characteristic (ROC) curves calculated at different BED levels considering the two observers.

The ROC curves comparison performed using the DeLong test has reported no significant difference in the predictive performance of ERI_{TCP} to varying of the observer for all the BED levels analyzed. In particular, a p-value of 0.41 was obtained comparing the ROC curves in case of 14 Gy, $p = 0.77$ in case of 28 Gy, $p = 0.74$ in case of BED = 42 Gy, $p = 0.63$ for BED = 54 Gy and $p = 0.42$ for BED = 62 Gy.

The values in terms of predictive performance obtained for ERI_{TCP} to varying of the BED levels are reported in Table 4.

Table 4. Indicators of the predictive performance of the early regression index (ERI_{TCP}) index in the case of cervical cancer at different BED levels.

BED	AUC (95% CI)	Best Cut-Off	Sensitivity	Specificity	Youden Index
14 Gy	0.80 (0.51–1)	149.5	90.9	80	0.71
28 Gy	0.84 (0.58–1)	96.0	90.9	80	0.71
42 Gy	0.80 (0.53–1)	54.0	90.9	80	0.71
54 Gy	0.74 (0.47–1)	31.5	90.9	60	0.50
62 Gy	0.78 (0.53–1)	16.4	81.8	80	0.62

The values of sensitivity and specificity in Table 4 are referred to the discrimination obtained when the best threshold is considered. Figure 3 reports the values of the ERI_{TCP} to the BED values showing the highest predictive performance (BED = 28 Gy) considering the two observers.

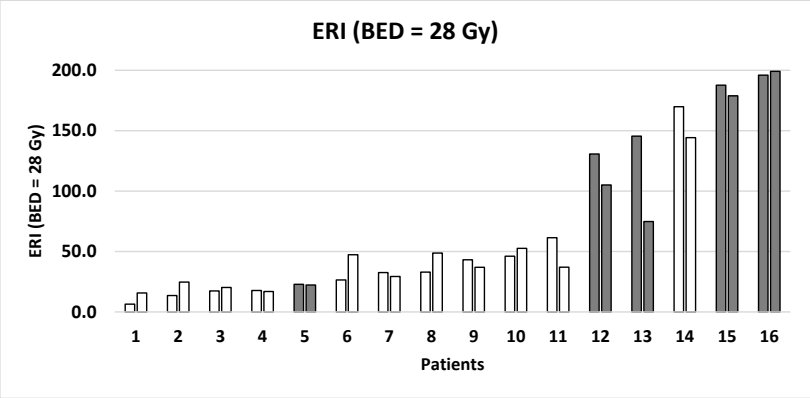

Figure 3. ERI_{TCP} values calculated at the most significant BED level for both observers (one column the highest predictive performance (BED = 28 Gy), no significant difference was observed using the DeLong's test (all *p*-values were >0.05).

As regards the tumor volume at simulation, an AUC value of 0.80 (0.57–1) was obtained, with no significant difference with respect the ROC curve calculated at BED = 28 Gy.

4. Discussion

This study investigated the use of ERI_{TCP} as pCR predictor in CC patients undergoing nCRT, analyzing MR images acquired using a low field MRgRT unit.

Being a morphological parameter, ERI_{TCP} can predict the response to nCRT by modelling the tumor volumetric regression during the treatment, simply using the information due to the volumetric variation of the tumor during the therapy: This makes ERI_{TCP} easy to use and generalizable to MR images acquired using different techniques and imaging parameters, as already demonstrated in the framework of rectal cancer [22,23,35].

One of the peculiarities of this study is represented by the possibility to correlate image-based parameters directly to histopathological data, being quite uncommon in the context of CC, as generally

the patients affected by this disease are addressed to brachytherapy and not to surgery, not allowing comparisons with histopathological ground truth.

The limited dimension of the population analyzed in this hypothesis generating study does not allow to draw definitive conclusions regarding the clinical use of this index, although it is interesting to observe that the predictive performance of this parameter is high and persists between independent observers.

The highest ERI_{TCP} performance in predicting pCR was observed when a BED value of 28 Gy was reached, with an AUC of 0.84, a sensitivity of 0.91 and a specificity of 0.8: The high value of sensitivity reported by this index may allow to successfully identify the patients that will undergo complete response since the second week of nCRT, avoiding unnecessary overtreatments and paving the way towards effective treatment personalization.

Although the DeLong's test did not report statistically significant differences between the ROC curves calculated at different timings (probably due to the reduced number of cases analyzed), it is interesting to observe that the most significant ERI_{TCP} timing identified for CC is the same observed for rectal cancer, regardless the obvious biological and histological differences that make the shrinkage pace not comparable in the two scenarios: This could be one of the reasons why the threshold value identified as best-cut off (96) is very different from the value of 13 observed in the rectal cancer experience [22,23].

A second study including an external cohort of patients is therefore recommended to validate the findings reported in this preliminary experience and confirm the most suitable timing and BED value. Unfortunately, the collection of homogeneous cohorts of patients affected by CC and undergoing nCRT will be particularly challenging, as most of these patients are generally addressed to brachytherapy, according to international guidelines [5].

5. Conclusions

This hypothesis generating study demonstrated that the use of the ERI_{TCP} can be extended to the context of CC, maintaining high levels of discriminative performance.

If validated on larger cohort of patients, the use of this index can represent a valuable tool to personalize the treatment strategy in the context of the CC, moving towards the anatomical and functional preservation of the irradiated tissues.

Author Contributions: Conceptualization: D.C. and C.F.; methodology: D.C., C.F., S.B.; software: L.P.; validation A.R., M.C., F.C., and V.D.L.; formal analysis: D.C., A.N.; investigation: C.V., M.N.; data curation: C.V., B.F., R.A.; writing—original draft preparation, D.C., A.P.; writing—review and editing G.C., L.B., S.B.; supervision: M.A.G., V.V., L.I. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest related to the present work.

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