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INCORPORATING INDIVIDUAL EARLY RESPONSE IN THE DOSE-EFFECT RELATIONSHIP OF COMPLETE PATHOLOGICAL RESPONSE FOLLOWING NEO-ADJUVANT RADIO-CHEMOTHERAPY FOR RECTAL CANCER

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Abstract

Purpose: To develop and externally validate a model predicting pathological Complete Response (pCR) in rectal cancer patients treated with neo-adjuvant radio-chemotherapy (RCT). The approach combines the classical Logit dose-effect curve with individual early response assessed by MRI during RCT.

Methods: The dose-response model incorporating the Early Regression Index (ERI) was derived from two published datasets. A population-averaged dose-response curve was obtained by fitting data from a recent meta-analysis. Then, an ERI-based model for pCR prediction was fit to 95 patients treated at XXX; ERI was incorporated as a dynamic dose-modifying factor (dDMF) in the Hill model,

based on EQD2 and including the time factor. The model was validated on an external cohort of 132 patients treated at XXX with standard and dose-escalated schedules. Calibration plots, AUC, and Average Precision were used to assess performance. Recalibration refined predictions for the external cohort.

Results: The final Hill model showed best-fit values of TD50=52.2 Gy, dDMF= (0.89 + 0.02*ERI), and steepness k = 5.91+0,11*ERI. The validation cohort had a pCR rate of 35.6%. Agreement between prediction and observed rates was high (offset = 0, slope = 0.84). Discriminative ability was robust (AUC 0.77; AP 0.65 vs 0.356 for baseline). ERI-stratified dose-pCR relationships confirmed predictive value across four ERI categories: highly responsive (ERI 1–6.9, pCR 65%), moderately responsive (6.9–13.1, 55%), poorly responsive (13.1–36, 14% and 35%), and non-responsive (>36, 0%). Predictions aligned with results using median ERI values per group.

Conclusions: The ERI-dose model was validated on an external cohort with distinct RT regimens. Dose escalation of 8.5 EQD2 Gy in moderate-to-good responders corresponds to an increase of approximately 20% in pCR, while no benefit was reported in non-responders. These findings highlight the model's potential for personalizing RT protocols by optimizing dose escalation based on ERI.

Keywords: personalised RT, Adaptive RT, pCR

Introduction

The management of locally advanced rectal cancer has significantly evolved, with neoadjuvant chemoradiotherapy (nCRT) now a key treatment[[1,2]]. This approach has proven effective in tumor downstaging and improving local control rates. A considerable number of patients experience a

pathological complete response (pCR), meaning no viable tumor cells are found in the surgical specimen. This result has led to interest in the "watch and wait" strategy, allowing some patients to avoid radical surgery while maintaining a good quality of life [3–9].

Despite ongoing studies, identifying suitable patients for this approach remains challenging. Meanwhile, advancements in radiation delivery have enabled dose-escalation strategies that promise better outcomes. Specifically, delivering a boost dose to residual tumors after early regression may effectively reduce severe side effects by targeting smaller treatment volumes [10–12].

Identifying patients likely to achieve a pathologic complete response (pCR) is a key research goal, especially to improve pCR rates through dose escalation and to avoid surgery for some patients. While clinical predictors such as baseline tumor volume, cancer stage, and distance from the anal verge have been proposed, they lack the necessary accuracy for reliable clinical decision-making. More advanced methods, including molecular markers like gene expression profiles and circulating tumor DNA [13,14], show promise but are often limited by cost, accessibility, and inconsistent standardization across institutions.

Image-based assessments of early response to neoadjuvant chemoradiotherapy (nCRT) are valuable, as rapid tumor regression has been well-documented [1,4,15–18]. The early regression index (ERI) effectively predicts pCR outcomes by combining initial tumor volume and regression measured through high-contrast MRI imaging[19–23]. This MRI-derived biomarker can potentially be used in other nCRT contexts, as seen in recent studies involving gynecological and esophageal cancers [24,25].

The existence of a dose-effect relationship for pathological complete response (pCR) is well-established [10,26]. However, developing a model that incorporates individual responses into the dose-effect curve would be extremely valuable. This would enable personalized treatment, including tailored dose prescriptions. The primary objective of this study was to develop a model combining prescription dose and ERI to predict the likelihood of achieving pCR. This model was further tested in an independent prospective cohort that underwent ERI-based dose intensification [20].

Materials and Methods

The development of a model combining radiobiological principles with information derived from conventional imaging was carried out through three key steps, using data from three different sources:

1. A population dose-response model was computationally derived through a comprehensive literature review [26] analyzing pathological complete response (pCR) in patients with rectal cancer who received varying doses of radiotherapy.
2. The personalized dose + ERI model was created by computationally integrating the logistic regression from the first step with a previously established ERI-dependent pCR model developed using data from an internal cohort (n=95) at XXX [19].
3. Finally, the combined model was validated using an external cohort of patients treated at XXXX (n=132) [20,24,27,28].

To specify, this combined model was designed for predicting the pCR in patients with GTV reduction at mid RT. In patients exhibiting minimal tumor volume reduction throughout radiotherapy, the method proposed by Fiorino et al. for esophageal cancer can be adopted to estimate the ERI [25].

We have graphically illustrated the entire workflow process in Figure 1. The characteristics of the population referred to item 2 were reported elsewhere [19], while the ones concerning item 3 from XXXXX are summarized in the Supplementary Materials.

Population dose-effect model

A population-averaged dose-response curve for pCR prediction was extrapolated using the data from the recent meta-analysis by Hall et al. [26]. First, we reasonably assumed a logistic regression to

describe the relationship between pCR probability and the prescribed dose, converted to Equivalent Uniform Dose to 2 Gy (EQD2) using an α/β value of 5 Gy. To estimate the dose coefficient for the logistic regression model, we linearized the equation and applied a fit to the data derived from the four studies analyzed by Hall. This involved taking the logit of the probability, expressed as $logit(P) = ln(P/(1-P)) = b_0 + b_1 * D$, thereby transforming the problem into a linear regression between logit(P) and D. By performing this linear regression, we were able to obtain the constant related to this population study, $b_{0_{pop}}$, and the coefficient for the prescription dose, b_D , defining the dose-response curve as follows:

$$pCR(D_{EQD2}) = \frac{1}{1+e^{-(b_{0_{pop}} + b_D * D_{EQD2})}} \quad (1)$$

Patient-Specific Customization

All patients of the training cohort, as reported by Broggi et al [19], were treated with daily image-guided radiotherapy in 18 fractions: in the first 12 fractions, 27.6 Gy (2.3 Gy/fr) were delivered on PTV, obtained by expanding the Clinical Target Volume (CTV, as defined in [18]). In the last six fractions, an adaptive concomitant boost was planned using high-resolution T2w MRI at the 9th fraction, delivering 3.0 Gy/fr on the residual tumor (GTV) expanded by 0.5cm (PTVadapt): the resulting total dose was 45.6 Gy and 41.4 Gy to PTVadapt and PTV, respectively. Concomitant chemotherapy consisted of Oxaliplatin (OXA) 100 mg/m2 on days -14, 0 (being day 0 at the start of radiotherapy), and +14, and 5-Fluorouracil (5-FU) 200 mg/m2/d or Capecitabine (from February 2015 on) 825 mg/m2 twice daily from day -14 to the end of radiotherapy. For these patients, we had access to detailed information about disease regression during treatment, including ERI as measured at mid RT, based on high-resolution T2w MRI available before RT (V_{pre}), and at mid RT (V_{mid}).

The ERI was calculated as follows based on the ratio of tumor volumes:

$$\text{ERI} = -\ln\left[(1 - {}^{V_{mid}}/_{V_{pre}})^{V_{pre}}\right]$$

A higher ERI, reflecting a poorer response lowers the predicted probability of a pathological complete response (pCR) for a given dose. In the paper by XXXXX [19], a logistic model relating PCR with ERI was assessed as:

$$pCR(ERI) = \frac{1}{1 + e^{-(b_{0_{ERI}} + b_{ERI} * ERI)}}$$

Coefficients of this regression were integrated in the constant $b_{0_{pop}}$ in formula (1), explaining part of its value through the ERI effect, the remaining value can be imputed to other impacting variables not yet integrated in the model, $b_{0_{eff}}$,:

$$b_{0_{pop}}(ERI) = b_{0_{eff}} + b_{0_{ind}}(ERI) = b_{0_{eff}} + b_{0_{ERI}} + b_{ERI} * \text{ERI} \quad (2)$$

Thus, the personalized logistic regression equation becomes:

$$pCR(D_{EQD2}, ERI) = \frac{1}{1+e^{-(b_{0_{pop}}(ERI) + b_D * D_{EQD2})}} \quad (3)$$

We then modified the model, converting it to a Logit EQD2 model with a time-factor correction, as described by Thames et al. [29]. A time-factor γ of 0.60 Gy/day, accounting for repopulation effects [30], was used. Of note, the Hall et al. meta-analysis considered patients treated with 1.8 Gy/fr, while XXX analyzed data from hypofractionated schemes. The constant $b_{0_{eff}}$was computed using the information coming from the same XXX et al. paper, i.e., 50% of pCR probability was reached once ERI = 6.9 and Prescribed Dose = 52.2 Gy (converted into EQD2 and with time factor), thus $TD_{50}(6.9) = 52.2\ Gy$.

After calibrating the model on the XXXX population, we converted the logistic regression into a Hill equation with ERI acting as a dynamic Dose Modifying Factor (dDMF) for the pCR dose, evolving

the static use of DMF for binomial factors as proposed in [31] and considering as normalization the $TD_{50}(6.9)$ instead of the usual TD50(factor = 0):

$$pCR(D_{EQD2}, ERI) = \frac{1}{\left(1 + dDMF(ERI) * \frac{TD_{50}(6.9)}{D_{EQD2}}\right)^{k(ERI)}}$$

and parameters are described as follows:

$$\begin{cases} TD_{50} = -\frac{b_{0_{pop}}(ERI)}{b_D} \\ dDMF\ (ERI) = {TD_{50}(ERI)}/{TD_{50}(6.9)} \\ k\ (ERI) = 1.6 * m \\ m = -\frac{1}{b_{0_{pop}}(ERI)} \end{cases}$$

This procedure resulted in a series of sigmoid-shaped curves, each corresponding to a different ERI value.

Validation Study

The validation cohort (XXX) comprised a first set of 64 patients treated with simultaneous integrated boost (SIB) delivering 55 Gy/25 fractions to the GTV (EQD2 = 57.4 Gy). Concomitant chemotherapy with capecitabine chronomodulated (1650 mg/mq)/5-fluorouracil or an intensification schedule with capecitabine (1300 mg/mq) plus oxaliplatin (60 mg/mq) was prescribed for all patients, according to the clinical stage and general condition. ERI was retrospectively calculated at mid-RT using low-field MRI on an MR-Linac, and data were previously used to confirm the value of ERI in pCR discrimination [21]. From the same institution, we merged additional data from 68 patients enrolled in a prospective clinical trial [20], in which patients with ERI >13.1 received dose escalation (boost regimen: 10 fractions at 2.2 Gy followed by 15 fractions at 2.57 Gy, EQD2=65.9 Gy). Patients with ERI ≤ 13.1 continued standard treatment. This also allowed us to test whether the increase in pCR

from the dose escalation could be described by our model. To present pCR results as a function of dose and dose escalation, we divided the data in 4 group using three ERI cut-off: 6.9 representing the TD50 for the ERI model in xxx et al, 13.1 indicating the clinical value for dose escalation in the XXXX trial and 36 representing the third quartile in the XXXX population and a possible threshold for clinical applicability of dose escalation as suggested in xxxx et al.

Calibration plots, Area Under the Curve (AUC), and Average Precision metrics were used to assess model performance in the external population. In addition, model recalibration (calibration in the large, Platt Scaling, Isotonic regression and Model updating) were performed by adjusting the intercept and slope of the logistic regression function to minimize the difference between observed and predicted pCR probabilities. We reported more details on recalibration approaches and performances in SM3.

Results

The meta-analysis by Hall and colleagues analysed 3298 patients treated in 2000–2013 from the National Oncology Data AllianceTM (NODA), a pooled database of cancer registries from >150 US hospitals. Eligible patients received nCRT followed by surgery. They had complete data on treatment start dates, radiotherapy dose, clinical tumor (cT) and ypT stage, and number of positive nodes at surgery. The dose was analyzed as a categorical variable with patients divided into four groups: patients treated with <45 Gy (defined as 36–43.2 Gy), 45 Gy, and 50.4 Gy were compared to patients receiving 54 Gy as the reference category. Rates of pCR varied between 9% and 19%. The review reported the Odds Ratio for each group *vs* the reference category. We utilized the pCR ratio, the dose prescription in EQD2, and the number of events per subgroup to establish four data points with error bars. Using linear regression, we determined the parameters $b_{0_{ERI}} = 5.79$ and $b_{ERI} = 0.08$ needed

to define equation (1). Details on data, fit, and coefficient errors are reported in Supplementary Materials 1 (SM1).

Once assumed from XXX et al. that in the ERI model (for patients receiving three chemotherapy cycles) $pCR(52.2\ Gy, 6.9) = 50\%$, $b_{0_{eff}}$ resulted in 4.17, and equation (3) became:

$$pCR\left(D_{EQD2}, ERI\right) = \frac{1}{1 + e^{-(3.69 - 0.07 * ERI + 0.08 * D_{EQD2})}} =$$

, showing an OR = 0.93 for ERI (0.91-0.96) and 1.08 (1.06-1.10) for prescription dose.

To better understand the impact of the individual radiosensitivity constant on the pCR, $b_{0_{pop}}(ERI)$, we converted the logistic regression into a Hill equation with ERI acting as a dDMF, resulting in $TD_{50} = 52.2\ Gy$, $dDMF(ERI) = 0.02 * ERI + 0.89$, and $k(ERI) = 5.91 + 0{,}11 * ERI$. Regarding validation, the distributions of Vpre and Vmid values were 29.3 cc (1.8-135.5 cc) and 17.1 cc (0.9-91 cc), respectively. Consequently, the median ERI for the XXXXX cohort was 31.6 (1.25-187.5), and pCR was 35.6%. For a direct comparison, we reported the same values from the xxxxxx population: Vpre (30.8 cc, 2.3-283.0), Vmid (11.2 cc, 0.1-242.0), ERI (14.1, 0.1-555), and pCR (33.9%).

In Table 1, we reported further details on development and validation populations. From the resulting calibration plot in Fig. 2, we estimated a calibration in-the-large = 0, indicating no systematic under/overestimation, and a slope of 0.84, suggesting a slight overestimation at higher probabilities. Coefficients were computed from the absolute values of predicted probabilities and observed outcomes across the entire range of predictions (red circles in Figure 3), i.e., without averaging predicted probability and observed pCR (blue points in Figure 3). The agreement between the predictions and the actual data was evaluated using the Hosmer-Lemeshow (HL) test; p-value = 0.54, indicating good model calibration. The model demonstrated moderate discriminative ability, with an AUC of 0.77. Additionally, the Average Precision (AP) was 0.65, a significant improvement over the

random model's AP of 0.36, underscoring the model's robust ability to accurately identify positive events.

The agreement between clinical results and predicted pCR curves stratified according to ERI (Fig. 3) demonstrated consistent performance across four ERI categories:

- highly responsive (ERI range 1–6.9, mean value 4.5, sigma = 1.6), pCR=65%,
- moderately responsive (ERI 6.9–13.1, mean value 10.3, sigma = 1.3), pCR=55 %,
- poorly responsive (ERI 13.1–36, mean value was 22.3 with sigma = 6.5), pCR=14% (standard) and 35% (escalated protocol),
- non-responsive (ERI>36, mean value = 74.4 and sigma = 38.9), pCR=0% in both regimens.

After recalibration [32], the model's performance improved with AUC = 0.79, PR-AUC = 0.69 and a slope was 0.99 with offset = 0 (see Supplementary Materials). The new coefficients indicated that ERI had a more significant impact on pCR than initially modelled with a reduction of 10 in ERI corresponding to an OR = 0.37 vs 0.50 in the developed model.

Discussion

The innovative adaptive treatment approach introduced at XXXXX [12] is proving to be an effective strategy for enhancing the likelihood of pCR by escalating radiation doses to the residual tumor during the latter stages of radiotherapy (RT). By targeting the residual tumor, we accomplish significant sparing of normal tissues, as opposed to conventional boosting methods based solely on initial tumor volume, thanks to considerable shrinkage observed in most patients. This was preliminary explored by in silico dose-escalation studies [33], using NTCP models to estimate the risk increase; while the experience by trial xxxxxxx suggested the feasibility of a dose escalation in the dose range here reported [20].

Integrating a reliable imaging biomarker, such as the ERI, in a dose response model empowers us to customize treatment based on individual patient response. The XXXXX study [20], with its

preliminary results discussed within the validation cohort, well exemplifies this concept by utilizing ERI to identify poor responders, enabling targeted dose intensification on the residual tumor after halfway through RT. The establishment of dependable predictive tools grounded in individual ERI assessments is essential for refining and effectively delivering higher doses to residual tumors, maximizing the anticipated gains in pCR rates. Results from the current investigation are notably promising, indicating the capability to predict pCR probabilities based only on tumor volumetry taken before and during RT. The validation results demonstrate that the model accurately predicted outcomes for the XXXX population, although the coefficients were trained on a different dataset. Precisely, the XXXXX study's outcomes were successfully forecasted, revealing a "failure" to increase pCR rates among poor responders (ERI > 36) and an approximate 20% uptick in pCR rates among moderate responders (ERI between 13 and 36). Furthermore, results for responding patients (ERI<13) who did not receive further intensification aligned precisely with the model's predictions.

The application of two distinct MRI modalities across the two cohorts (high-resolution T2-weighted MRI vs. low-field MRI in an MRI_Linac) further substantiates the model's robustness. This evidence indicates that ERI is highly reliable and minimally affected by contouring uncertainties, as previously established [23] in the context of locally advanced rectal cancer. While robustness may be somewhat reduced in other scenarios, such as early rectal cancer or the recent application of ERI in oesophageal cancer [25], the overall strength of the ERI approach remains compelling. After rigorous fitting and validation, we confidently apply our model to quantify the expected increase in the probability of pCR with dose escalation, tailored to each patient's response profile. This application enables the following:

1. Personalized predictions of pCR probability based on the planned dose and the observed early treatment response, as assessed by ERI;
2. Accurate estimation of the potential benefits of dose escalation for individuals, empowering adaptive radiotherapy planning;

3. Effective risk stratification, allowing us to identify patients who are prime candidates for organ-preservation strategies and those who could benefit from intensified treatment.

Our predictions and findings indicate that intensifying the dose for most patients (i.e., those with an ERI of less than 36) is a rational strategy challenging the outdated "one-size-fits-all" approach to cancer management. This approach could enhance the clarity in identifying patients who can safely avoid surgery, leading to a more efficient allocation of healthcare resources.

Multi-institutional prospective studies spanning the full range of dose and ERI are needed to refine effect estimates, assess interactions, and confirm clinical utility. Indeed, as a limitation, our model was validated in cohorts in which dose escalation was applied only to patients with unfavourable predicted pCR; whether escalation benefits in good responders remains unproven and requires prospective evaluation with safety and functional endpoints. The base dosimetric model derives from the Hall et al. population, reflecting conventional fractionation and lower EQD2 than some contemporary schedules, and may not be transportable across institutions with differing fractionation, concurrent chemotherapy, and planning workflows, requiring local validation and recalibration. However, the dose–response relationship identified by our model is consistent with that reported by Appelt et al., showing comparable TD50 values (71.7 Gy vs. 70.5 Gy, derived from –b0pop/bD in equation 1), computed using the same α/β value for EQD2 correction and a similar gamma parameter for tumor cell repopulation. Their cohort included patients treated with either 60 Gy in 30 fractions or 50.4 Gy in 28 fractions, both followed by a 34 Gy brachytherapy boost [34].

Additional limitations include potential variability in ERI acquisition/timing, retrospective elements, and limited power for toxicity and organ-preservation outcomes.

Conclusion

This study presents a clinically actionable ERI-based model to personalize radiotherapy in rectal cancer. In our cohort, protocolized dose escalation for patients with unfavorable ERI and intermediate-to-low predicted pCR increased the probability of pCR. This effect was evident in patients who showed at least minimal tumour-volume reduction during treatment, whereas no benefit was observed in those with stable volumes, consistent with model predictions. The model demonstrates stable discrimination and good calibration, supporting real-time decisions; implementation requires early-response imaging to compute ERI, integration into the planning workflow, and multidisciplinary oversight to balance oncologic control, toxicity, and organ preservation.

The model's positive performance in the unfavorable-ERI cohort strongly motivates validation in moderately or highly responding populations, where small-volume dose escalation with focal boosts may permit a larger fraction of patients to achieve pCR.

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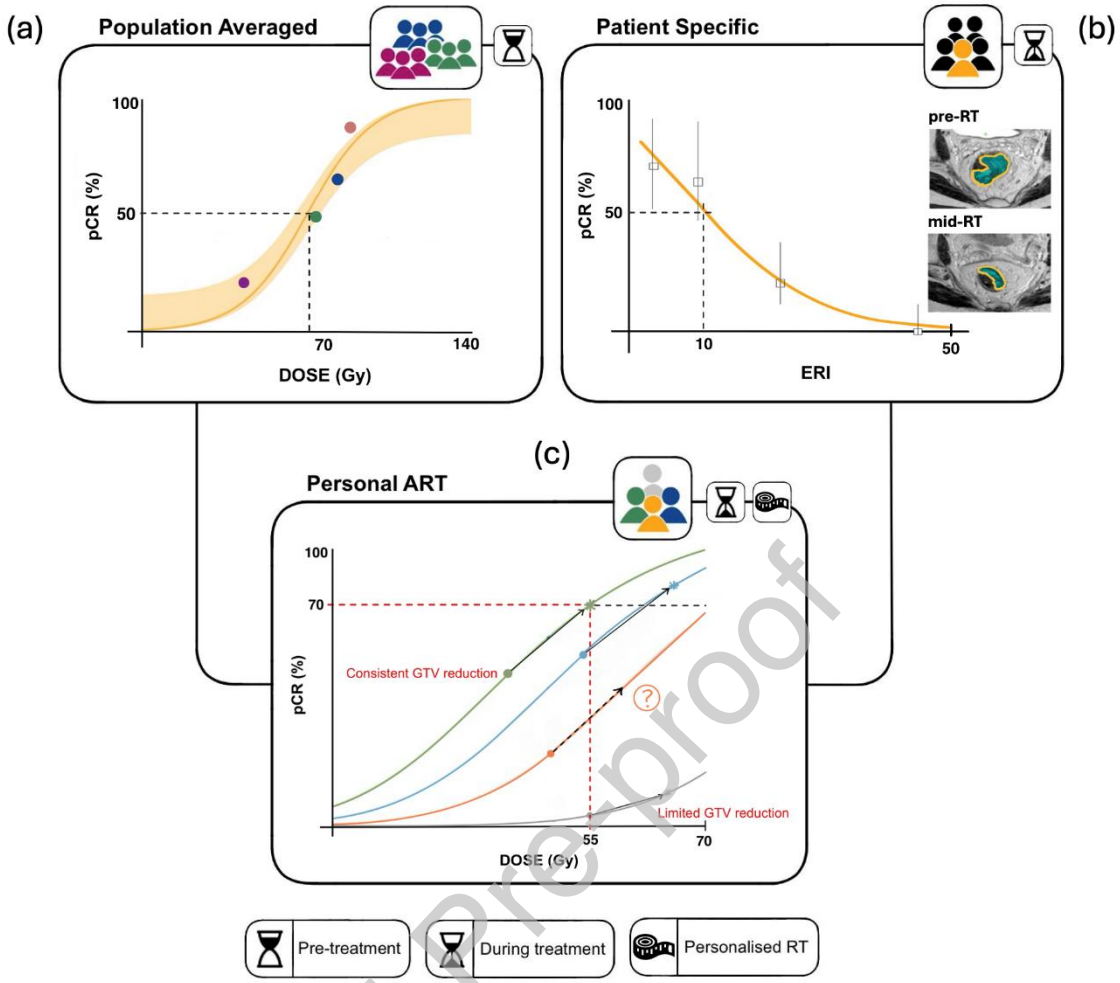

Fig.1: Characteristics of (a) Dose, (b) ERI, and (c) Dose + ERI model in the prediction of the pathological Complete Response for rectal cancer patients. The dose model is an averaged representation of the population pCR with the advantage of predicting a pCR probability before RT planning, the ERI model can be of help for monoinstitutional applications were prescription dose is homoegenous but any predicition is postponed at half of RT, the combined model offers the opportunity to define an adaptive RT at half of the total fractions increasing the pCR in responsive patients.

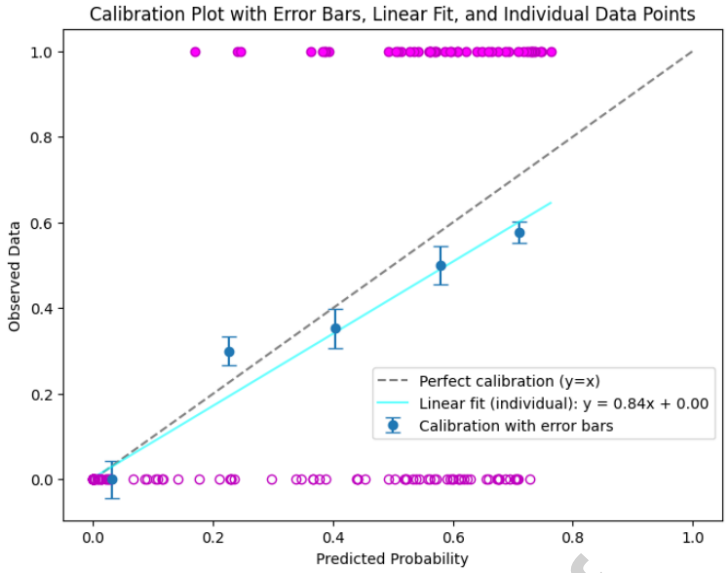

Figure 2: Calibration plots for the ERI-Dose model in the external validation cohort. Purple circles indicate the pCR (0-1) as a function of the model probability, blue line is the linear fit and blue points represented the averaged rates with error bars.

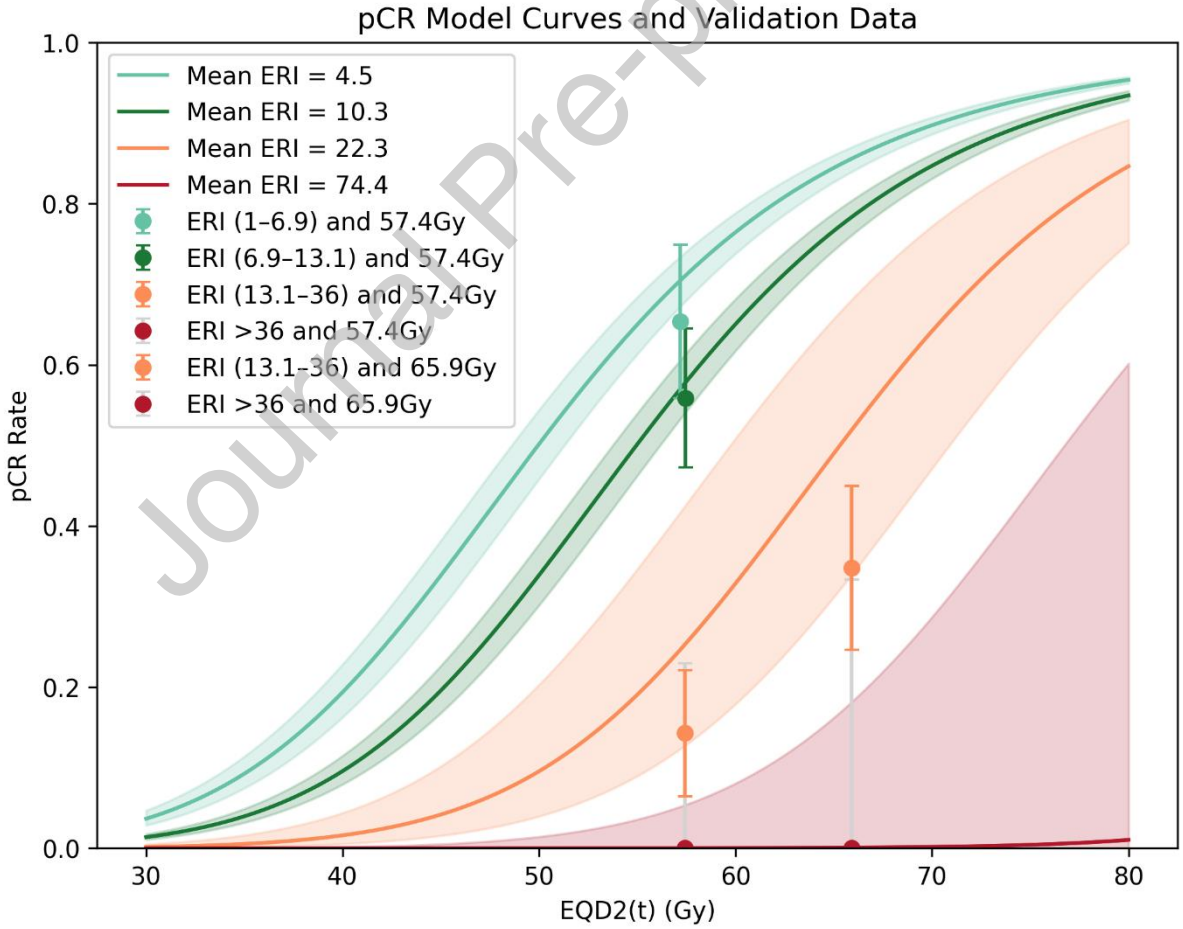

Figure 3: Predictive Model Curves and validation points in the 4 responders groups. Curves are described as a function of the EQD2(t) and considering the average ERI in each group with error bars equal to ± **σ**. For validation points the error bars represent the standard error of the mean, while for pCR = 0, the error was estimated using the formula sqrt(1/n).

	Development Cohorts		Validation Population	
	Hall et al	**XXXXX Trial**	**Retrospective Study**	**XXXXX Cohort**
Patients number	3298	59	43	64
ERI≤ 13.1	n.a	26 (44%)	12 (28%)	32 (50%)
ERI range	n.a	0.1-550	1.2-187.5	3.2 -55.63
RT dose at GTV	36 to 54 at 1.8 Gy/fr	27.6 Gy at 2.3 Gy/fr + 18 Gy at 3 Gy/fr from 12th fr	55 Gy at 2,2 Gy	55 Gy at 2.2 Gy Or 60.1 Gy in 2.57 Gy/fr from11thfr
pCR	15%	33.9%	27.9%	37.5%
cT **2** **3** **4**	 12.2% 79.3% 5%	 8.5% 81.4% 8.5%	 14% 50% 30%	 9% 84% 6%
cN **0** **+**	 53% 41.5%	 16.9 81.4	 23% 77%	 78% 22%
Concurrent chemotherapy 5-FU/cape Capox/Folfox other	 86% 2% 12%	 100%	 56% 34%	 98% 2%
Age	61 (52-69)	62 (37-78)	62.4 (38-86)	68 (31-94)

Table 1: Description of disease stage and treatment characteristics in cohorts used to define and validate the model incorporating prescription dose and early regression index (ERI).