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Original Research Article

Accurate outcome prediction after neo-adjuvant radio-chemotherapy for rectal cancer based on a TCP-based early regression index

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ABSTRACT

Background and purpose: An early tumor regression index (ERI_{TCP}) was previously introduced and found to predict pathological response after neo-adjuvant radio-chemotherapy of rectal cancer. ERI_{TCP} was tested as a potential biomarker in predicting long-term disease-free survival.

Materials and methods: Data of 65 patients treated with an early regression-guided adaptive boosting technique (ART) were available. Overall, loco-regional relapse-free and distant metastasis-free survival (OS, LRFS, DMFS) were considered. Patients received 41.4 Gy in 18 fractions (2.3 Gy/fr), including ART concomitant boost on the residual GTV during the last 6 fractions (3 Gy/fr, D_{mean}: 45.6 Gy). Chemotherapy included oxaliplatin and 5-fluorouracil (5-FU). T2-weighted MRI taken before (MRI_{pre}) and at half therapy (MRI_{half}) were available and GTVs were contoured (V_{pre}, V_{half}). The parameter $ERI_{TCP} = -\ln[(1 - (V_{half}/V_{pre}))^{Vpre}]$ was calculated for all patients. Cox regression models were assessed considering several clinical and histological variables. Cox models not including/including ERI_{TCP} (CONV_model and REGR_model respectively) were assessed and their discriminative power compared.

Results: At a median follow-up of 47 months, OS, LRFS and DMFS were 94%, 95% and 78%. Due to too few events, multivariable analyses focused on DMFS: the resulting CONV_model included pathological complete remission or clinical complete remission followed by surgery refusal (HR: 0.15, p = 0.07) and 5-FU dose >90% (HR: 0.29, p = 0.03) as best predictors, with AUC = 0.75. REGR_model included ERI_{TCP} (HR: 1.019, p < 0.0001) and 5-FU dose >90% (HR: 0.18, p = 0.005); AUC was 0.86, significantly higher than CONV_model (p = 0.05). Stratifying patients according to the best cut-off value for ERI_{TCP} and to 5-FU dose (> vs <90%) resulted in 47-month DMFS equal to 100%/69%/0% for patients with two/one/zero positive factors respectively (p = 0.0002). ERI_{TCP} was also the only variable significantly associated to OS (p = 0.01) and LRFS (p = 0.03).

Conclusion: ERI_{TCP} predicts long-term DMFS after radio-chemotherapy for rectal cancer: an independent impact of the 5-FU dose was also found. This result represents a first step toward application of ERI_{TCP} in treatment personalization: additional confirmation on independent cohorts is warranted.

1. Introduction

The assessment of biomarkers able to individually predict the outcome of radio-chemotherapy (RCT) followed by curative surgery in locally advanced rectal cancer is a topic of high interest due to the large potentials in individualizing therapy [1–3] including the choice of treatment intensification, surgery omission and additional systemic therapies. Predictive models based on clinical/histological characteristics [1,2,4] as well as on pre-treatment imaging-based [5–7], histological [1,2], or "omics" [8,9] features have been explored during the last years. On the other hand, the early pathological response is also known to be a predictor of outcome, in particular the occurrence of pathological complete remission (pCR) at surgery [10,11]. More recently, the evidence

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that the tumor substantially shrinks in most patients during and after the treatment pushed several groups to exploit this measurable effect to develop predictive models based on tumor regression. Quite importantly, tumor regression measured by MRI [12–19] was recently applied to predict the pathological response to the treatment with relevant potentials in selecting patients that may avoid surgery, and in dramatically improving their quality of life compared to patients submitted to surgery [20–22].

Tumor regression during therapy, although less investigated [17–19,23–25], has been shown to be correlated with pathological response as well, with the advantage to give a prediction during the treatment and consequently to increase the potentials of response-driven treatment personalization. Moreover, tumor regression during RCT has also been successfully exploited by our group to implement early-regression guided adaptive boosting therapy [19,23] with great potentials for treatment intensification aiming to increase the rate of pCR [26], similarly to what recently reported with image-guided brachytherapy boosting [27]. More in general this approach (i.e., escalating the dose on the residual tumor after early response assessed by proper imaging techniques) seems to be highly promising even outside the rectal cancer scenario [28].

Within the described context, we previously suggested a general TCP Poisson-like formula, combining the initial tumor volume and tumor regression, quantified by high-contrast MRI imaging, assessing an early regression index (named ERI_{TCP}) as a robust in-vivo radiobiological biomarker able to accurately predict the pathological response [19]: in fact, ERI_{TCP} was able to discriminate the pathological response in a group of 65 patients previously treated with RCT within our early regression guided ART boosting study, showing AUC around 0.80 and very high negative predictive power (>90%).

In current study, we wished to test the potential of ERI_{TCP} in predicting the long-term clinical outcome of the same group of patients, aiming to extend the potential applications of ERI_{TCP} in treatment individualization. In addition, the performance of ERI_{TCP} in predicting outcome were compared against conventional clinical and histological parameters.

2. Material and methods

2.1. Patients and treatment

A group of 65 patients with rectal adenocarcinoma whose clinical and imaging data were fully available, was considered: characteristics of the patients have already been reported [19] and are summarized in the Supplementary material. In short, all patients were treated within our ART observational study approved by the Institute Board [23,25] in the period 2009–2016: all patients previously signed an informed consent. The concomitant chemotherapy consisted of Oxaliplatin 100 mg/m^2 on days −14, 0 (being day 0 the start of radiotherapy), and +14, and 5-fluoroacil (5-FU) 200 mg/m^2/d from day −14 to the end of radiotherapy. All patients were treated with daily image-guided Helical Tomotherapy 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 [23]), of 0.5 cm isotropically. In the last 6 fractions, an adaptive concomitant boost was planned using MRI imaging information performed at the 9th fraction, delivering 3.0 Gy/fr on the residual tumor (GTV) expanded by 0.5 cm (PTV_{adapt}): the resulting total dose was 45.6 Gy and 41.4 Gy to PTV_{adapt} and PTV respectively. After surgery, the tumor regression grade (TRG) was defined according to the residual viable cells (RVC) percentage compared with fibrosis [10]: TRG0 = no regression, TRG1 = RVC >75%, TRG2 = RVC 50–75%, TRG3 = RVC <50%, and, TRG4 = no RVC, also defined as pathological complete response (pCR). Forty-three patients received post-operative chemotherapy, at discretion of the oncologist, mostly using oxaliplatin and/or capecitabine.

2.2. MRI volumetry

High resolution T2-weighted MRI images before the start of Radiotherapy (MR_{pre}) and at the 9th fraction (MR_{mid}) were available. All scans were obtained with 1.5 Tesla scanners (Achieva, Philips Medical Systems, Best The Netherlands). Details of MRI acquisition are shown elsewhere [18]: MRI studies included morphological high resolution turbo spin echo T2-weighted sequences oriented according to tumour's orthogonal planes.

Tumor volumes were contoured by a single radiation oncologist previously tutored by a radiologist on axial images at MR_{pre} (V_{pre}) and MR_{mid} (V_{mid}); the consistency between this observer and a skilled radiologist expert of rectal cancer imaging was previously verified and found to be satisfactory [19].

2.3. Early regression index definition: ERI_{TCP}

Based on the familiar Poisson-based Tumor control probability (TCP) modeling [29] ERI_{TCP} was previously introduced [19] as:

$$ERI_{TCP} = -\ln\left[\left(1 - \left(V_{mid}/V_{pre}\right)\right)^{Vpre}\right] \quad (1)$$

In short, the formula well represents the expected early response based on the approximation that the tumor volume is proportional to the number of clonogens [29,30]. After the delivery of a dose equal to D, the resulting tumor volume V may be approximated by the surviving fraction of tumor cells and the fraction of cells killed but not yet removed [30]. Formula (1) is robustly valid if assuming as negligible the inter-patient variability of the exponential delay of tumor cells removal. The logarithmic transformation was introduced just to obtain positive numbers between 0 (strong response) and few tens (poor response). As mentioned, ERI_{TCP} was previously confirmed to be a strong predictor of the pathological response in the considered population [19].

Despite ERI_{TCP} is based on tumor volumetry only, it has to be considered as an intrinsically radiobiological index being directly associated, within the above mentioned limits, with the probability of tumor control in a classical Poisson-based TCP approach.

2.4. End-point definition and analyses

For all patients, information regarding overall, loco-regional relapse and distant metastasis-free survival (OS, LRFS, DMFS) was available. Time-to event or to last follow-up/death was calculated from the end of Radiotherapy.

Kaplan-Meyer curves and univariate and multivariate Cox proportional hazards regression were used.

First, a number of clinical and histological variables were considered as potential predictors of the three considered outcome, including: age, sex, Oxaliplatin dose, 5-FU dose, time to surgery, clinical stage, adjuvant chemotherapy, pCR, pCR or clinical complete response (cCR) followed by surgery refusal, RVC <5%, RVC <10%). Univariate analyses were carried out for all three end-points while multivariate analysis with backward variable selection was performed only for DMFS, due to the number of available events (see later); the resulting multivariate model (i.e., not considering TCP_{ERI}) was named CONV_model. Then, ERI_{TCP} was tested as predictor of the three end-points and a multivariate model for DMFS was similarly assessed and named REGR_model.

The discriminative power of CONV_model and REGR_model was assessed through the analysis of the receiver operating charac-

teristic (ROC) curves. Area under the curve (AUC and its 95% confidence limits), sensitivity and specificity were considered to quantify the performance of the models. Finally, AUCs of the two models were compared according to the DeLong method [31]. The robustness of models in discriminating relapses was assessed by bootstrap (1000 cycles) to correct AUC values for optimism. Analyses were performed using MedCalc Software (v. 12.1.4.0, Medcalc Softare bvba); the bootstrap validation was performed using MatLab software.

3. Results

3.1. Outcome results

The median duration of the treatment was 25 days and the time between radiotherapy and surgery was 11 weeks (range: 7–19 weeks). Two patients showing cCR at MRI_{post} refused surgery while 63 patients were operated: 20/63 (32%) patients experienced pCR and 30% and 36.5% of patients showed an RVC >10% and 5% respectively. The mean tumor volumes values were: V_{pre} = 32.6 - cm^3 (range 2.3–268 cm^3); V_{mid} = 15.6 cm^3 (range: 0.1–159 cm^3).

With a median follow-up of 47 months (range: 12–91), 62/65 patients were alive; overall, loco-regional relapses were 3/65 (2 out of 3 were local) and distant relapses were 13. The actuarial rates at 47 months for OS, LRFS and DMFS were 94.1% ± 3.4%, 94.7% ± 3.0% and 77.8% ± 5.5%. Due to the very limited number of events for OS and LRFS, the multivariable analyses were restricted to DMFS.

3.2. Predictors of outcome; CONV_model for DMFS

Likely due to the limited number of events, no variables were associated to a worse outcome for OS and LRFS at univariable analysis. Concerning DMFS, several variables were associated with an increased risk of relapse and were summarized in Table 1. The strongest predictors were 5-FU dose and "pCR or cCR + surgery refusal". The resulting CONV_model (Table 2) found "pCR or cCR + surgery refusal" and 5-FU dose >90% as independent predictors. The discriminative power of the model was moderately high, with AUC = 0.75 (95%CI: 0.62–0.85).

3.3. ERI_{TCP} as predictor of outcome: REGR_model for DMFS

Despite the very small number of events, higher ERI_{TCP} values were associated to a worse OS (p = 0.011) and LRFS (p = 0.033), as shown in Fig. 1. ERI_{TCP} was also strongly predictive of DMFS (p < 0.001): the resulting REGR_model included ERI_{TCP} (HR: 1.019, p < 0.0001) and 5-FU dose >90% (HR: 0.18, p = 0.005) as independent predictors (Table 2). AUC was 0.86 (95%CI: 0.76–0.94), significantly higher than the corresponding value for CONV_model (p = 0.05).

Table 1
Parameters significantly (P < 0.05, Univariable Cox model) associated to improved overall, local relapse-free and distant relapse-free survival (OS, LRFS, DRFS).

OS	HR	(95%CI)	p-value
ERI_{TCP}	1.016	1.004–1.028	0.011
LRFS			
ERI_{TCP}	1.014	1.001–1.024	0.033
DRFS			
5-FU dose	0.964	0.937–0.992	0.014
5-FU dose >90%	0.25	0.08–0.76	0.015
pCR or cCR + surgery refusal	0.15	0.02–1.00	0.05
ERI_{TCP}	1.017	1.008–1.025	0.0001

Table 2
Multivariable models for the prediction of distant relapse-free survival (DRFS) not including (CONV) or including (REGR) the TCP-based early regression index (ERI_{TCP}).

CONV MODEL	HR	(95%CI)	p-value
5-FU dose >90%	0.29	0.09–0.89	0.031
pCR or cCR + surgery refusal	0.15	0.02–1.17	0.072
p = 0.006, AUC = 0.75 (0.62–0.85)			
REGR MODEL	HR	(95%CI)	p-value
5-FU dose >90%	0.18	0.05–0.59	0.005
ERI_{TCP}	1.019	1.010–1.028	<0.0001

P < 0.0001, AUC = 0.86 (0.76–0.94).

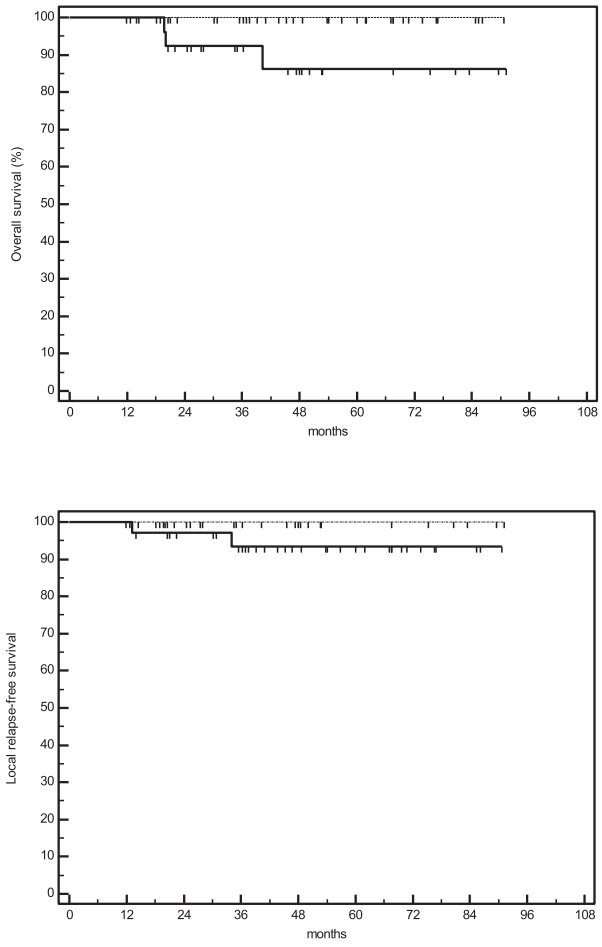

Fig. 1. Impact of ERI_{TCP} on Overall Survival (a) and Local Relapse-free Survival (b): patients are splitted in two groups according to ERI_{TCP} > or ≤17.7 (best cut-off value). Differences are significant (p-values equal to 0.01 and 0.03 respectively).

The value of AUC of REGR model corrected for optimism (after bootstrap based validation) was 0.85 (1SD:0.057), confirming the solidity of the result.

In Fig. 2, ROC curves for DMFS of the two models are shown. When grouping patients according to the best cut-off value for ERI_{TCP} (equal to 17.7, i.e., lower value means better response), 33 patients were below this value. If grouping the patients according to the presence of two/one/zero factors (ERI_{TCP} <17.7 and/or 5-FU dose >90%) the number of events in the three groups was 0/31, 10/29 and 3/5 respectively. The corresponding DMFS plot is shown in Fig. 3: DMFS at 47 months was equal to 100% vs 69% (±9.4%) vs 0% for the three groups respectively (p = 0.0002).

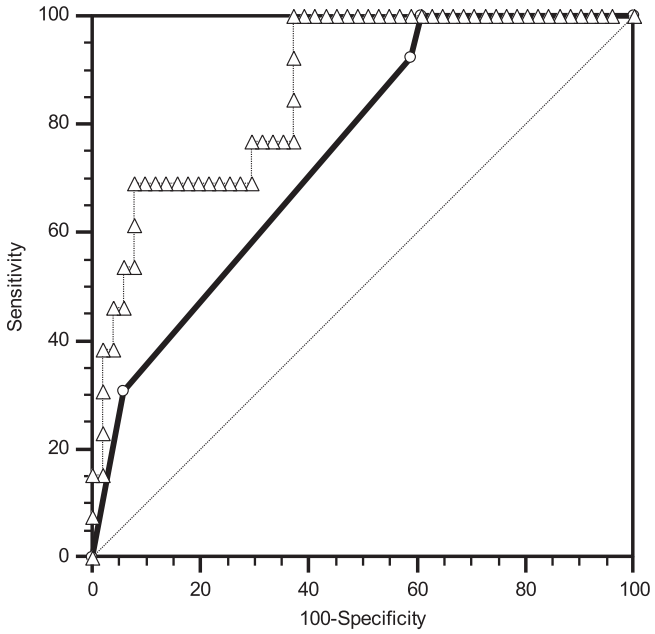

Fig. 2. The AUCs referred to the two predictive models of Distant relapse-free Survival reported in Table 2 (CONV and REGR, without and with the inclusion of ERI_{TCP} in the considered variables) are shown. The difference between the two curves is significant (p = 0.05).

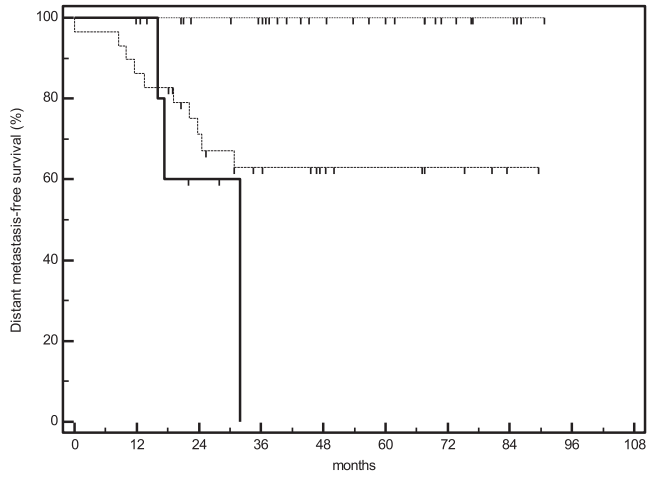

Fig. 3. Distant metastasis-free survival against ERI_TCP <17.7 (best cut-off) and 5-FU dose >90% (full/almost full delivered drug dose): patients are grouped according to the presence of two (n = 31), one (n = 29, 4 pts with 5-FU <90% and 25 with ERI_TCP >17.7) and zero (n = 5) positive factors (p = 0.0002).

4. Discussion

This is the first study that reported association between a previously introduced early regression TCP-based index (ERI_{TCP}) and the long-term outcome of a cohort of rectal cancer patients treated with neo-adjuvant radio-chemotherapy.

Despite the low number of events, ERI_{TCP} was found to be associated to overall survival and local relapse-free survival with better performance compared to the pathological response as assessed after surgical resection. Due to the number of events, the most robust result concerns the risk of metastatic relapses: ERI_{TCP} was the strongest predictor of metastasis-free survival while the pathological response resulted of borderline significance. An independent effect of the delivered chemotherapy dose (5-FU) was also found resulting in two-variable models predicting DMFS including this parameter (i.e., 5-FU >90% of the prescribed dose) and pCR (+cCR and surgery refusal) or, alternatively, ERI_{TCP}.

The two models (named CONV and REGR) performed differently, being REGR model more robust and significantly more discriminative of distant metastasis relapses, reflecting the better discriminative power of ERI_{TCP} compared to the pathological response.

Importantly, ERI_{TCP} incorporates the initial volume and the early response that may be considered as an "in-vivo" quantitative measurement of the sensitivity of the tumor clonogens to the treatment: both factors (initial volume and early response) are rationally included in the parameter, resulting in a more robust predictor; ERI_{TCP} was previously found to predict the pathological response on the same group of patients with high discriminative power and negative predictive value higher than 90% [19]. Another factor explaining these successful results is likely to be the inclusion of oxaliplatin two weeks before and during radiotherapy: this drug reasonably enhanced the effect of early tumor shrinkage [32,33], improving the discriminative ability related to any biomarker based on tumor regression. A strong early response is also expected to reduce the impact of tumor delineation uncertainty on the quantification of the response, as previously shown [19].

While ERI_{TCP} promises to be a potential tool for therapy personalization (i.e., identifying patients candidates to avoid surgery, treatment intensification aimed to increase pCR and/or sphincter preservation, patients candidates to avoid surgery), being able to discriminate in advance the pathological response, current results add light to the meaning of early response during therapy with respect to outcome, including the pattern of distant relapses.

The association between ERI_{TCP} and DMFS is not a proof of causality, which remains to be demonstrated. The fact that patients with lower ERI_{TCP} (i.e., strong response during therapy) have a lower probability to experience distant relapses could mean that responding tumors (including the combined impact of the initial number of clonogens, as done by ERI_{TCP}) are more sensitive to therapy and/or less aggressive and consequently less subject to metastatic spread. Others reported correlation between the pathological response at surgery and long-term survival as well as distant relapse-free survival [1,2,10,11].

On the other hand, one could argue that the (local) strong response could reduce any risk of subsequent metastatization, although this seems to be unlikely to be detected in a relatively small group of patients, due to the effective elimination of the residual tumor cells by surgery.

Another intriguing possibility is that a strong local response could reflect into an immune reaction helping in reducing the risk of (or postponing) any metastatic spread [34].

In any case, ERI_{TCP} was found to be a promising index to predict patient's outcome early during treatment delivery: this may also open other potentials for treatment personalization, more aimed to reduce the risk of distant relapses in patients with high ERI_{TCP} values. This could reflect into more aggressive and extensive systemic treatment for these patients, partly corroborated by the detrimental effect of any incomplete drug delivery (5-FU). For instance, ERI_{TCP} could in theory help to determine what is the best sequence (chemotherapy followed by radio-chemotherapy or radio-chemotherapy followed by chemotherapy) and the best number of chemotherapy cycles when following a total neoadjuvant therapy approach [35].

On the contrary, in case any causality between high ERI_{TCP} and risk of distant relapses exists (direct or mediated by the immune system), one could try to increase the fraction of responding patients (i.e., with lower ERI_{TCP}) by intensifying the loco-regional treatment, for instance through dose escalation to the residual tumor; in this case, the response-driven adaptive boosting

approach proposed by our group [23] as well as other similar approaches with external beams or brachytherapy [26,27] could be followed. In any case, dose intensification with personalization of the delivered dose based on ERI_{TCP}, could in principle be effective in increasing the number of complete response, potentially increasing the number of patients who could avoid surgery dramatically, with a consequent relevant impact on their quality of live [20,22]. Proper clinical trials based on patient's stratification using ERI_{TCP} to personalize treatment may be hypothesized.

On the other hand, a note of caution is still necessary: given the limited number of events, current analysis may be associated to some risk of overfit. Then it has to be considered as a first step toward the demonstration of the clinical utility of ERI_{TCP}. The internal validation by bootstrap suggested that the risk of overfit in current analysis should be limited and this is particularly true for REGR model, showing to be highly robust.

In any case, more validations on larger, and possibly external cohorts, is mandatory in order to corroborate the results of current study: of note, the application of ERI_{TCP} to an external cohort is currently in progress.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.07.001.

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