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Original article

A TCP-based early regression index predicts the pathological response in neo-adjuvant radio-chemotherapy of rectal cancer

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ABSTRACT

Purpose: Introducing a radiobiological index based on early tumor regression during neo-adjuvant radio-chemotherapy (RCT, including oxaliplatin) of rectal adenocarcinoma and testing its discriminative power in predicting the tumor response.

Methods: Seventy-four patients were treated with Helical Tomotherapy following an adaptive (ART) protocol (41.4 Gy/18 fr, 2.3 Gy/fr) delivering a simultaneous integrated boost on the residual tumor in the last 6 fractions up to 45.6 Gy. T2-weighted MRI were taken before (MRI_{pre}) and at mid (MRI_{mid}) therapy and the corresponding tumor volumes were considered (V_{pre},V_{mid}). The "Early Regression Index" ($ERI_{TCP} = -\ln[(1-(V_{mid}/V_{pre}))^{V_{pre}}]$) was introduced and its discriminative power was assessed in terms of AUC, sensitivity/specificity, positive/negative predictive value (PPV/NPV). Two end-points were considered: (a) pathological complete response (pCR) or clinical complete response followed by watch-and-wait, (cCR); (b) limited response (residual vital cells (RVC) in the surgical specimen >10%).

Results: Complete data were available for 65 patients: pCR, cCR and RVC >10% were 20, 2 and 19 respectively. The discriminative power of ERI_{TCP} was moderately high (AUC = 0.81/0.75 for /pCRorcCR/RVC >10% respectively, $p < 0.0005$). ERI_{TCP} was highly sensitive (86–89%) with very high NPV (90–94%). The discriminative power of ERI_{TCP} was confirmed on a subgroup of 44/65 patients when considering tumor volumes delineated by a skilled radiologist.

Conclusion: A radiobiologically consistent index based on early regression showed high performances in predicting the pathological response after neo-adjuvant RCT for rectal cancer with relevant potentialities for ART/treatment customization.

A non-negligible fraction of patients treated with long-term radio-chemotherapy (RCT) before curative surgery for locally advanced rectal cancer experiences a complete pathological response (pCR) at the time of surgery, typically ranging between 10% and 20% [1–4]. Moreover, there is a clear evidence that the tumor substantially shrinks in many patients during and after the treatment and this effect was used to develop adaptive boosting approaches with the aim of escalating the dose to the residual tumor, both with external beams and with brachytherapy [5–7]. Tumor regression measured by MRI [8–18] was recently applied to predict the pathological response to the treatment.

A reliable prediction of the pathological response based on tumor regression after RCT could help in selecting patients that may avoid surgery, with potentially dramatic improvements in their quality of life compared to patients submitted to surgery [19–21].

Our group clinically implemented an adaptive (ART) concomitant boost protocol escalating the dose to the residual tumor (imaged at half-therapy) in the last 6 fractions within a moderately hypo-fractionated regimen delivered with daily image-guided Tomotherapy and concomitant chemotherapy, including oxaliplatin [5,22,23]. All patients treated following this protocol were submitted to MRI before the treatment (for planning) and at half therapy (for the ART planning) [18] and this represents a quite rare opportunity to model the early individual response.

Most studies on the relationship between MRI-based volume regression and pathological response considered the volume regression at the end of the treatment, while very few studies dealt

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with the regression during therapy: in a preliminary analysis on 48 patients treated with our protocol, the volume at half-therapy and the regression at half therapy showed a moderately high discriminative value when considering pCR [18]. On the contrary, Joye et al. [17] found a poor discriminative value of volume regression at half therapy in predicting pCR in 85 patients treated to 45 Gy, 1.8 Gy/fr with concomitant chemotherapy, not including oxaliplatin.

The limit of any "phenomenological" approach in assessing the value of MRI-based volumetry and/or tumor regression is the intrinsic lack of generalizability: models based on statistical correlation cannot be easily extended outside the clinical scenario where they are derived and need extensive independent validation [24]. The purpose of the present study was to introduce a radiobiologically based predictive index incorporating the early tumor regression and to apply it to the patients treated with our ART protocol. Such approach should intrinsically be more easily generalizable, being based on a robust, radiobiologically based, explanation of tumor regression.

Material and methods

Patients and treatment

Seventy-four consecutive patients with rectal adenocarcinoma treated within our ART prospective study in the period 2009–2016 were considered; details are described elsewhere [6,23]. In short, 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 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 the Clinical Target Volume (CTV, as defined in [6]), of 0.5 cm isotropically. In the last 6 fractions, an adaptive concomitant boost was planned on CT/MRI imaging performed at 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 [4]: TRG0 = no regression, TRG1 = RVC >75%, TRG2 = RVC 50–75%, TRG3 = RVC <50%, and, TRG4 = no RVC, also defined as pathological complete response (pCR). Complete clinical response followed by watch-and-wait (i.e.: skipping surgery) were also registered (cCR). The characteristics of the patients are shown in Table 1.

Table 1
Characteristics of the patients (n = 65).

Sex (M:F)	43:22
Age (median)	35–75 years (61 years)
ECOG PS (median)	0–1 (1)
cT	T2: 5 (7.7%) T3: 56 (86.2%) T4: 4 (6.2%)
cN	N0: 10 (15.4%) N+: 55 (84.6%)
Tumor location	Upper third: 9 (13.8%) Middle third: 23 (35.4%) Lower third: 26 (40.0%) n.a.: 7 (10.8%)
Grading	1: 3 (4.6%) 2: 33 (50.8%) 3: 6 (9.2%) n.a.: 23 (35.4%)
Cranio-caudal extension (MRI)	1.2–9 cm (median 5 cm)

MRI protocol and tumor delineation

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

Tumor volumes were contoured by a single skilled radiation oncologist previously tutored by a radiologist on axial images at MR_{pre} (V_{pre}), MR_{mid} (V_{mid}) and MR_{post} (V_{post}). For the purpose of current study, only the information at mid therapy was considered.

Robust modeling of tumor regression based on Poisson's statistics

Tumor control probability (TCP) may be robustly modeled by Poisson's statistics [25–27]: if N_{pre} and N are the number of cells before and after the delivery of a dose equal to D, TCP may be expressed by:

$$TCP = (1 - S(D))^{N}_{pre} \quad (1)$$

where $S(D) = N/N_{pre}$ is the surviving fraction after the delivery of D.

In first approximation, the tumor volume V_{pre} may be considered to be proportional to N_{pre} [25,26]. 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: the removal of this second component is generally assumed to follow an exponential law [26].

If we neglect the inter-patient variability of the exponential delay of tumor cells removal (i.e.: considering it as roughly constant), formula (1) may translate into:

$$TCP = K \times (1 - (V/V_{pre}))^{V}_{pre} \quad (2)$$

where K is a constant value. If the timing of the assessment of V, the chemotherapy protocol and the total delivered dose are the same for all patients, the TCP value of formula (2) would be proportional to the remaining cells at the end of therapy and, likely, to the pathological response.

Then, we postulated that the following radiobiological figure of merit (Early regression index, ERI), should predict the pathological response:

$$ERI_{TCP} = -\ln[(1 - (V_{mid}/V_{pre}))^{V_{pre}}] \quad (3)$$

The logarithmic transformation was introduced just to obtain positive numbers between 0 (strong response) and few tens (poor response), being its argument expected to be a very small number.

End-point definition and analyses

The discriminative power of ERI_{TCP} was assessed through the analysis of the receiver operating characteristic (ROC) curves. Area under the curve (AUC and its 95% confidence limits), sensitivity and specificity were considered to quantify the performance of the models. In addition, the corresponding positive and negative predictive values (PPV and NPV) were assessed in correspondence of the best cut-off value of AUC, corresponding to the lowest p-value. The following end-points were considered:

(1) pCR or cCR (followed by watch-and-wait)
(2) limited response (defined by RVC >10%)

In order to test the reliability of our approach with respect to delineation, volumetric data previously collected on a subgroup of 44 patients based on the contours delineated by an expert

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