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

Claudio Fiorino a,⇑, Paolo Passoni b, Anna Palmisano c, Calogero Gumina b, Giovanni M. Cattaneo a, Sara Broggi a, Alessandra Di Chiara c, Antonio Esposito c, Martina Mori a, Monica Ronzoni d, Riccardo Rosati c, Najla Slim b, Francesco De Cobelli c, Riccardo Calandrino a, Nadia G. Di Muzzio b

a Medical Physics, San Raffaele Scientific Institute, Milano, Italy
b Radiotherapy, San Raffaele Scientific Institute, Milano, Italy
c Radiology, San Raffaele Scientific Institute, Milano, Italy
d Oncology, San Raffaele Scientific Institute, Milano, Italy
e Gastroenterology Surgery, San Raffaele Scientific Institute, Milano, Italy

A R T I C L E   I N F O

Article history:
Received 10 April 2019
Revised 1 July 2019
Accepted 1 July 2019
Available online 3 July 2019

Keywords:
Rectal cancer
Magnetic resonance imaging
Modeling
Tumor control probability
Adaptive radiotherapy

A B S T R A C T

Background and purpose: An early tumor regression index (ERITCP) was previously introduced and found to predict pathological response after neo-adjuvant radio-chemotherapy of rectal cancer. ERITCP 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 (MRIpre) and at half therapy (MRIhalf) were available and GTVs were contoured (Vpre, Vhalf). The parameter ERITCP = $-\ln\left(1 - \frac{V_{\text{half}}}{V_{\text{pre}}}\right)^{V_{\text{pre}}}$ was calculated for all patients. Cox regression models were assessed considering several clinical and histological variables. Cox models not including/including ERITCP (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 ERITCP (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 ERITCP and to 5-FU (> vs <90%) resulted in 47-month DMFS equal to 100%/69%/0% for patients with two/one/zero positive factors respectively (p = 0.0002). ERITCP was also the only variable significantly associated to OS (p = 0.01) and LRFS (p = 0.03).

Conclusion: ERITCP 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 ERITCP in treatment personalization: additional confirmation on independent cohorts is warranted.

⇑ Corresponding author at: Medical Physics, San Raffaele Institute, Via Olgettina 60, 20132 Milano, Italy.
E-mail address: fiorino.claudio@hsr.it (C. Fiorino).

https://doi.org/10.1016/j.ctro.2019.07.001
2405-6308/© 2019 Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 ERITCP) as a robust in-vivo radiobiological biomarker able to accurately predict the pathological response [19]; in fact, ERITCP 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 ERITCP in predicting the long-term clinical outcome of the same group of patients, aiming to extend the potential applications of ERITCP in treatment individualization. In addition, the performance of ERITCP 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/m² on days −14, 0 (being day 0 the start of radiotherapy), and +14, and 5-fluorouracil (5-FU) 200 mg/m²/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 (PTVadj): the resulting total dose was 45.6 Gy and 41.4 Gy to PTVadj 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 (MRpre) and at the 9th fraction (MRmid) 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 MRpre (Vpre) and MRmid (Vmid); 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: ERITCP

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

\[ \text{ERITCP} = -\ln \left( 1 - \left( \frac{V_{\text{mid}}}{V_{\text{pre}}} \right) \right) \]  

(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, ERITCP was previously confirmed to be a strong predictor of the pathological response in the considered population [19].

Despite ERITCP 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 for DMFS, due to the number of available events (see later); the resulting multivariate model (i.e., not considering TCPadj) was named CONV_model. Then, ERITCP 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 Software 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 MRIpost 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: \( V_{\text{pre}} = 32.6 \text{ cm}^3 \) (range 2.3–268 cm\(^3\)); \( V_{\text{mid}} = 15.6 \text{ cm}^3 \) (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. ERITCP as predictor of outcome: REGR_model for DMFS

Despite the very small number of events, higher ERITCP values were associated to a worse OS (\( p = 0.011 \)) and LRFS (\( p = 0.033 \)), as shown in Fig. 1. ERITCP was also strongly predictive of DMFS (\( p < 0.001 \)); the resulting REGR_model included ERITCP (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 (\( p = 0.05 \)).

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 ERITCP (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 (ERITCP <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 (\( p = 0.0002 \)).

Table 1

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

Table 2

| 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 |
| ERITCP     | 1.019    | 1.010–1.028 | <0.0001 |

P = 0.0001, AUC = 0.86 (0.76–0.94).

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

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 ERITCP compared to the pathological response.

Importantly, ERITCP 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; ERITCP 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 ERITCP 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 ERITCP and DMFS is not a proof of causality, which remains to be demonstrated. The fact that patients with lower ERITCP (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 ERITCP) 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, ERITCP 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 ERITCP 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, ERITCP 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 ERITCP 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 ERITCP) by intensifying the loco-regional treatment, for instance through dose escalation to the residual tumor; in this case, the response-driven adaptive boosting

4. Discussion

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

Despite the low number of events, ERITCP 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: ERITCP 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
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 ERITCP, 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 life [20,22]. Proper clinical trials based on patient's stratification using ERITCP 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 ERITCP. 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 ERITCP to an external cohort is currently in progress.

Declaration of Competing Interest

None.

Acknowledgment

The study was in part supported by an AIRC grant (IG18965)

Appendix A. Supplementary data

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

References

[1] Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. J Clin Oncol 2015;33(16):1797–808.
[2] Rödel C, Hofhnen R, Fokas E. Rectal cancer: neoadjuvant chemoradiotherapy. Best Pract Res Clin Gastroenterol 2016;30(4):629–39.
[3] Ryan JE, Warrier SK, Lynch AC, et al. Predicting pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. Color Rectal Dis 2016;18(3):234–46.
[4] Huh JW, Kim HR, Kim YJ. Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. Dis Colon and Rectum 2013;56(6):698–703.
[5] Taylor FGM, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY Study. J Clin Oncol 2014;32(1):34–43.
[6] Van Stiphout RGP, Lammering G, Buijse J, et al. Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging. Radiother Oncol 2011;98(1):126–33.
[7] Buleu P, Couwenberg A, Haustermans K, et al. Development and validation of an MRI-based model to predict response to chemoradiotherapy for rectal cancer. Radiother Oncol 2018;126(3):437–42.
[8] Jia H, Shen X, Guan Y, et al. Predicting the pathological response to neoadjuvant chemoradiation using untargeted metabolomics in locally advanced rectal cancer. Radiother Oncol 2018;128(3):548–56.
[9] Molinari C, Matteucci F, Caroli P, et al. Biomarkers and molecular imaging as predictors of response to neoadjuvant chemoradiation in patients with locally advanced rectal cancer. Clin Colorect Cancer 2015;14(4):227–38.
[10] Rödel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after radiochemotherapy of rectal cancer. J Clin Oncol 2005;23:8688–96.
[11] Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011;29(28):3753–60.
[12] Beets-Tan RGH, Beets GL. MRI for assessing and predicting response to neoadjuvant treatment in rectal cancer. Nat. Rev. Gastroenterol. Hepatol. 2011;11(8):480–8.
[13] Barbaro R, Fiorucci C, Tebala C, et al. Locally advanced rectal cancer: MR imaging in prediction of response after preoperative chemotherapy and radiation therapy, Radiology 2009;250:730–9.
[14] Locatelli P, Widder U, Lambregts DM, Maas M, et al. Rectal cancer assessment of complete response to preoperative combined radiation therapy with chemotherapy: conventional MR volumetry vs diffusion-weighted MR imaging. Radiology 2011;260:734–43.
[15] Patel UB, Brown G, Rutten H, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Annals Surg Oncol 2012;19(9):2842–52.
[16] Intven M, Mominikof M, Reenerd O, et al. Combined T2w volumetry, DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in locally advanced rectal cancer. Acta Oncol 2015;54(10):1729–36.
[17] Joyce I, Debuquoy A, Deroose CM, et al. Quantitative imaging outperforms molecular markers when predicting response to radiochemotherapy for rectal cancer. Radiother Oncol 2017;124:104–9.
[18] Palmisano A, Esposito A, Di Chiara A, et al. Could early tumor volume change assessed on morphological MRI predict the response to Chemoradiation therapy in locally advanced rectal cancer? Clin Radial 2018;73:555–63.
[19] Ficino C, Gunmi C, Passoni P, et al. A TCP-based early regression index predicts the pathological response in neo-adjuvant radio-chemotherapy of rectal cancer. Radioter Oncol 2018;128:564–8.
[20] Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–40.
[21] Habr-Gama A, Perez RO, Guilherme PSJ, Proscurshim I, Gama-Rodrigues J. Nonoperative approaches to rectal cancer: a critical evaluation. Sem Radiat Oncol 2011;21:234–9.
[22] Renehan AG, Malcomson LM, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174–83.
[23] Passoni P, Fiorino C, Slim N, et al. Feasibility of an adaptive strategy in preoperative radiotherapy for rectal cancer with image-guided tomotherapy: boosting the dose to the shrinking tumor. Int J Radiat Oncol Biol Phys 2013;87:67–72.
[24] Maggulli E, Fiorino C, Passoni P, et al. Characterisation of rectal motion during neoadjuvant chemoradiotherapy for rectal cancer with image-guided radiotherapy: implications for adaptive dose escalation strategies. Acta Oncol 2012;51(3):318–24.
[25] Raso R, Scalo E, Fiorino C, et al. Assessment and clinical validation of margins for adaptive simultaneous integrated boost in neo-adjuvant radiochemotherapy for rectal cancer. Phys Med 2015;31:167–72.
[26] Fiorino C, Cozzarini C, Passoni P. The promise of adaptive radiotherapy for pelvic tumors: “too high cost for too little result” or “a low cost for a significant result”? Acta Oncol 2016;55(8):839–42.
[27] Appelt AL, Paars J, Harlala K, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919–27.
[28] Boggreve AS, Mook S, Verheij M, et al. Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in isophegal cancer (PRIDE): a multicenter observational study. BMC Cancer 2018;18:1006.
[29] Johnson CR, Thames HD, Huang DT, et al. The tumor volume and clonogen number relationship: Tumor control predictions based upon tumor volume estimates derived from computed tomography. Int J Radiat Oncol Biol Phys 1995;33:281–8.
[30] Chetvoz AV. Tumor response parameters for head and neck cancer derived from tumor-volume variation during radiation therapy. Med Phys 2012;39:034101.
[31] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biomometrics 1988;44:837–45.
[32] Rödel C, Graeven U, Finkla R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2015;16:979–89.
[33] Flatmark K, Hole KH, Sarlen MG. Effect of oxaliplatin-containing neoadjuvant chemotherapy on tumor volume in locally advanced rectal cancer and sensitivity of surviving tumor cells to radiotherapy. J Clin Oncol 2013;31:3547.
[34] Vantouquette-Box C, Fornienni SC, Demaria S. Toward precision radiotherapy for use with immune checkpoint blockers. Clin Cancer Res 2018;24(2):259–65.
[35] Ludmir EB, Palta M, Willett CG, et al. Total neoadjuvant therapy for rectal cancer: an emerging option. Cancer 2017;123(9):1487–506.