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MRI tumor volume reduction rate vs tumor regression grade in the pre-operative re-staging of locally advanced rectal cancer after chemo-radiotherapy

Emanuele Neri[a,*], Elisa Guidi[a], Francesca Pancrazi[a], Maura Castagna[b], Elisa Castelluccio[b], Riccardo Balestri[c], Piero Buccianti[c], Luca Masi[d], Alfredo Falcone[d], Bruno Manfredi[e], Lorenzo Faggioni[a], Carlo Bartolozzi[a]

[a] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Unit of Diagnostic and Interventional Radiology, Pisa University Hospital, Italy
[b] Unit of Anatomy and Pathology, Pisa University Hospital, Italy
[c] Unit of Colorectal Surgery, Pisa University Hospital, Italy
[d] Unit of Oncology, Pisa University Hospital, Italy
[e] Unit of Radiotherapy, Pisa University Hospital, Italy

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ABSTRACT

Objective: To compare tumor volume reduction rate (TVRR) measured by MR volumetry after preoperative chemoradiotherapy (CRT) and pathological tumor regression grade (TRG) in locally advanced rectal cancer (LARC).

Material and methods: In total, 20 patients with LARC (cT3-T4) treated with CRT followed by Total Mesorectal Excision (TME) between April 2011 and April 2013 were analyzed retrospectively.

Pre- and post- CRT tumor volumes (MR volumetry) were measured on 3D MR sequences. TVRR was determined using the equation TVRR (%) = (pre-CRT tumor volume—post-CRT tumor volume) × 100/pre-CRT tumor volume. The downstaging (defined as ypT0-T2) of tumor mass was evaluated and the correlation between TVRR and TRG was calculated with the method proposed by Dworak using the Spearman rank test.

Results: The median TVRR was 77.3% (range, 26.4–99.3%); TVRR was >60% in 18 cases (90%) and in 8 of these patients (44.4 %) it was >80%. Downstaging of tumor lesions was obtained in 15 patients (75%). In 4 cases there was a complete tumor regression (TRG4) at histological examination and in the same patients there was also a TVRR > 80% measured by MR volumetry. A statistically significant correlation between TVRR and TRG ($r_s = 0.5466$, $p = 0.0126$) was observed.

Conclusion: TVRR after preoperative CRT correlates with TRG in LARC. The MR volumetry is a prognostic factor to estimate the tumor response after preoperative CRT. TVRR data may be an useful biomarker for tailoring surgery and postoperative adjuvant chemotherapy.

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1. Introduction

In patients with locally advanced rectal cancer (LARC) who undergo combined treatments, consisting of preoperative chemo-radiotherapy (CRT), surgery, and post-operative adjuvant chemotherapy, the earlier prediction of CRT responses is critical for tailoring subsequent treatments and increase the chance of a cure in an individual patient.

Since post-CRT tumor downstaging is one of the most important prognostic factors in LARC with preoperative CRT, it's necessary to understand the best strategy to evaluate and possibly quantify with measurable biomarkers the degree of tumor downstaging [1].

The currently accepted downstaging criteria consist in the measurement of two-dimensional (WHO, world health organization) or only one-dimensional (RECIST, response evaluation criteria in solid tumors) tumor diameters.

The estimation of pre- and post-treatment tumor size represents one important criterion to quantify the response to treatments, but

* Corresponding author at: Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Unit of Diagnostic and Interventional Radiology, Pisa University Hospital, Italy.
E-mail address: emanuele.neri@med.unipi.it (E. Neri).

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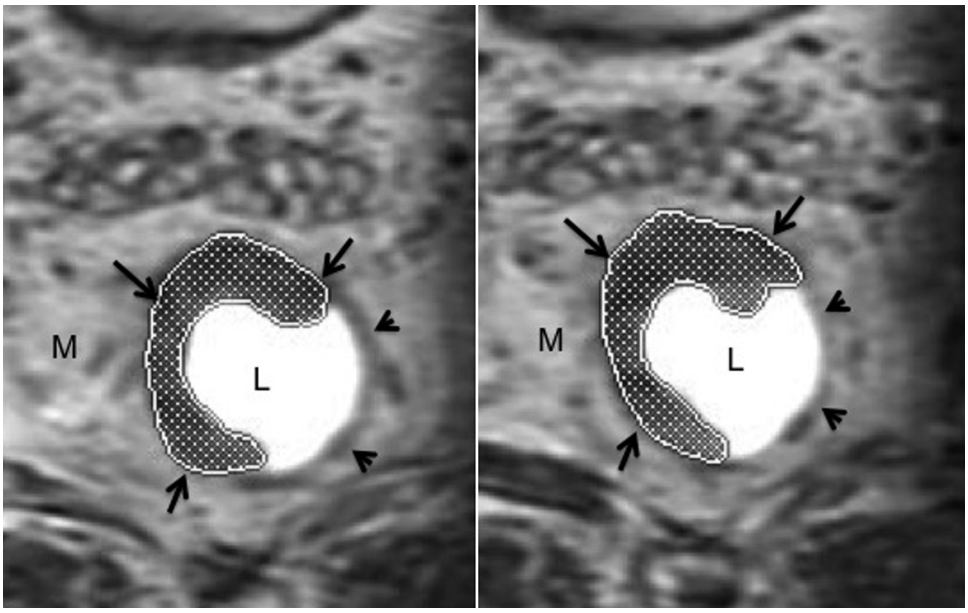

Fig. 1. Segmentation framework of a LARC located in the middle rectum (arrows). Mesorectum (M), rectal lumen filled by a water solution (L).

the two-dimensional measurements are subject to intrinsic errors, due to an irregular tumor shape, a non uniform treatment-related shrinkage, and the variability of manual measurements performed by the radiologist, that make it difficult to identify all subtle tumor size changes induced by CRT [2].

The pathological tumor regression grade (TRG), is based on a semi-quantitative scale (from 0, no response, to 4, complete pathological response), and is commonly used to estimate response to CRT in the surgical specimen [3–5].

The value of MRI in the assessment of TRG has been evaluated in a subgroup analysis (92 patients with pre- and post-treatment MR studies) of the MERCURY trial (magnetic resonance imaging in rectal cancer european equivalence study) [6]. The study showed that MRI predicts the disease free survival and overall survival of patients that undergo neoadjuvant therapy for rectal cancer. A further study of the same author showed that MRI correlates also with a favorable and unfavorable histopathological TRG [7].

Tumor volumetric reduction has been also addressed as a valuable prognostic biomarker of response to CRT; it can be measured in vivo by three-dimensional (3D) region-of-interest volumetry (MR Volumetry) since MRI is the unique, "in vivo", imaging tool that allows to precisely differentiate tumor borders from normal soft tissue, and therefore estimate tumor extent [8,9].

Therefore the so called "tumor volume reduction rate" (TVRR) after preoperative CRT, measured with MR volumetry, has been investigated as a predictive factor of response to treatment and a biomarker of patient's prognosis, and in patients with LARC, a correlation between high TVRR and favorable pathologic CRT responses was reported [10–13].

The objective of the present study was to investigate the correlation between TVRR and TRG after preoperative CRT, as a predictive factor of response to treatment in LARC.

2. Material and methods

2.1. Patients

This is a single institution prospective cohort study that included twenty patients, 13 male and 7 female, with mean age 62 years (range, 34–75 years), with locally advanced rectal cancer.

The inclusion criteria were histologically confirmed rectal adenocarcinoma, distal end of tumor located within 15 cm from the anal verge, locally advanced disease (cT3–4), tumor involvement of the mesorectal fascia, and/or positive nodal status evaluated with MR imaging with or without transrectal ultrasonography, preoperative treatment with a long course of neoadjuvant chemo-radiation treatment, no other coexistent malignancy within 5 years.

All patients underwent a staging protocol before preoperative CRT, that included chest X-ray, digital rectal examination, complete blood tests, colonoscopy, contrast enhanced computed tomography of the abdomen, external pelvic phased-array magnetic resonance imaging (MRI) and transrectal ultrasound. Those with a low quality MR exam (e.g., due to metal or motion artefacts) were excluded from the study.

2.2. Preoperative CRT

All patients received preoperative CRT. The total dose, which varied between 4500 and 5040 cGy, was divided into 5 fractions per week of 180 cGy each one. 3D conformal radiotherapy (3D-CRT) was performed using a linear accelerator (LINAC) with a beam of photons greater than or equal to 6 MV and, in accordance with the guidelines of the International Commission on Radiation Units and Measurements (ICRU 62); the treatment included the mesorectum, presacral, internal iliac and obturator lymph nodes, and external iliac nodes only in T4 stage.

Chemotherapy was administered concurrently with radiotherapy and consisted of oral administration of capecitabine 825 mg/mq × 2 die (Xeloda®, Roche) or intravenous injection of 5-fluorouracil 225 mg/mq/die.

2.3. MRI tumor volumetric analysis

All patients underwent 3T MRI (Discovery 750, General Electric, Milwaukee, Wis, USA) before CRT and 6 and 8 weeks after completion of CRT.

Three hours before the MR study, the patients performed a rectal cleansing with a water enema.

Before MR acquisition, the rectal lumen, was filled with a 60–100 mL water enema through a thin rectal catheter. Rectal filling was required to highlight the tumor borders within the lumen.

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