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original article

3D MRI segmentation and 3D circumferential resection margin evaluation for a standard rectal cancer assessment

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SUMMARY: **3D MRI segmentation and 3D circumferential resection margin evaluation for a standard rectal cancer assessment.**

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Aim. *Recent studies focused on rectal cancer suggested that a 3D imaging segmentation obtained from MRI data could contribute in the definition of the circumferential resection margin (CRM) and in the assessment of the tumor regression following neo-adjuvant treatments. Here, we propose a method for defining and visualizing the circumferential margins using 3D MRI segmentation; this methodology was tested in a clinical study comparing 3D CRM assessment vs standard MRI imaging.*

Patients and methods. *MRI scans performed before neo-adjuvant treatments were selected and reviewed. 3D mesorectal/tumor segmentations were obtained using Digital Imaging and COmmunications in Medicine (DICOM) data; CRMs were calculated using 3D volumes plus a color scale for the closest distances.*

Results. *3D reconstructions were possible in all selected cases and 3D images implemented by the color scale were positive for immediate CRM visualization. Statistical analyses comparing standard radiology disclosed that the degree of consistency, the reliability of ratings, the correlation and precision were optimal considering the overall cases, but lower in the CRM>0 mm sub-group.*

Conclusions. *This new method is not inferior comparing standard radiology; moreover, the imaging segmentation we obtained was highly promising and could be helpful in defining a standard CRM measurement, thus it could improve clinical practice.*

KEY WORDS: Rectal cancer - CRM - MRI - 3D imaging.

Introduction

The development of 3D medical models from standard radiology can be obtained from imaging scans using the Digital Imaging and COmmunications in Medicine (DICOM) software; this technology is evolving at a rapid pace and it is now disclosing highly promising data. Indeed, recent studies focused on colorectal cancer suggested that a 3D anatomical imaging segmentation could contribute in the definition of circumferential resection margins (CRM) and in the pre-operative assessment of the pathological tumor regression grade following neo-adjuvant therapy; although encouraging, the literature in this field is still, however, quite scant (1, 2). To date and as widely recognized, MRI is the gold standard in the pre-operative workout of rectal cancers; specifically, it is superior to CT scan in distinguishing low T3 from low T4 cancers and it has been acknowledged as the method of choice for the prediction of the CRM positivity (3). The sensibility, specificity and accuracy of the MRI for rectal cancer staging features have been improved by the use of the diffusion weighted imaging (DWI) protocols; however, the assessment of T3a tumors (invasion less than 5 mm) remains sub-optimal (4). In this field, the MERCURY clinical trial recommended to classify the CRM as potentially affected, if MRI scans show tumor within 1 mm from the mesorectal fascia (5) and the TNM staging of rectal

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tumors should classify pT3 cancers according to the distance from the mesorectal fascia (<1 mm, 1–5 mm, 5–15 mm, >15 mm) (6). On this basis, a further implementation of the pre-operative staging based on MRI scans that allows a univocal definition of CRM could impact surgical and clinical choices. We thus aimed to conduct a pilot clinical investigation using a 3D MRI segmentation (plus a color scale correlated to the distances between tumor and mesorectum) in order to evaluate the performance and the reliability of 3D evaluations in the assessment of CRMs. Secondary aim was to compare the proposed method with standard MRI scans.

Patients and methods

Study population

Patients who underwent pre-operative staging, neo-adjuvant treatment followed by surgical resection for rectal adenocarcinoma (< 12 cm from the anal verge) at our Institutions over the last 3 years were reviewed, independently of age and sex. Exclusion criteria were mucinous tumors (since it impairs diffusion MRI scans), cT2 tumors and cT4 cancers involving the sphincters (since this feature could impairs 3D segmentation). Of note, both Institutions been certified as a high volume center for colorectal cancer treatment by the Italian National Health Ministry (7). Internal Departments protocol usually begins upon patient's referral with a consultation in an MDT for planning the clinical strategy. Patients are usually staged locally using MRI and contrast enhanced CT scan for possible distant metastases. However, frequently patients perform radiological staging before being referred to our Hospitals; MRI scans are nevertheless reviewed by a GI radiologist, who assesses possible involvement of the mesorectal fascia (CRM) and the response after CHT-RT (8, 9). Patients presenting CRM<1 mm/≥cT3/cN+ are discussed in a multidisciplinary setting and scheduled for a CHT-RT neo-adjuvant treatment, followed by local re-staging with MRI scans. Subsequently, patients undergo surgical operation. For the purpose of this study, we investigated exclusively patients who performed radiological staging at our Departments. A formal IRB approval was not required because of the un-interventional retrospective design; however, a signed consent was obtained from all patients before the surgical and radiological procedures.

MRI technique and protocol

We selected for 3D MRI segmentation exclusively MRI images obtained before the beginning of neo-adjuvant treatments. MRI was performed using a 1.5-Tesla scanner (Sonata Siemens, Erlangen, Germany), with a phased-array body surface coil. To reduce intestinal motion artifacts, intramuscular injection of N-butyl scopolamine bromide, 20 mg, was administered to each patient, if not contraindicated, before beginning MRI scan. The standard imaging protocol consisted of axial Fast low-angle shot (FLASH) 2D T1 and axial Turbo Spin Echo (TSE) T2 weighted images of the whole pelvis. Thin-section (3-mm) Sagittal T2 weighted TSE images covering entire length of the rectum were acquired and used to plan axial scans. Thin-section (3-mm) axial images through the rectal cancer were performed perpendicular to the long axis of the tumor. For low rectal cancer, further oblique coronal T2 weighted TSE images along the long axis of the tumor were performed. DWI was acquired using three increasing b-values (50 to 400 to 800 s/mm^2) with echo planar imaging sequence with respiratory triggering. An ADC maps were derived automatically on a voxel-by-voxel basis by using commercially available software (Syngo; Siemens Medical Solutions). Subsequently, axial contrast-enhanced Fast low-angle shot (FLASH) 2D T1 weighted images with fat saturation, were acquired. For contrast-enhanced MRI, gadolinium-based paramagnetic contrast medium (Gd-DOTA, Dotarem, Guerbet, RoissyCdGCedex, France) (2ml/kg of body weight) was injected with a flow rate of 2 mL/s, followed by a 10 mL saline flush at the same rate. Axial T1 weighted images was performed 60 s after the contrast medium injection angled in identical planes of axial T2-weighted images and DWI, as previously described (8).

3D-imaging for CRM and segmentation

DICOM MRI images, acquired at 16 bits from HR T2 weighted axial scans have been selected. A 3D manual segmentation of the mesorectum, tumor and lumen has been processed using Slicer3D Sofware version 4.5 (10-14). Specifically, the physician has moved the cursor trough the boundary of the segmented region of interest (ROI) and by applying a set of reference-standard algorithms and graphical tools filled all the space enclosed. The boundary was delineated following the rule that a pixel belongs to the ROI when it is included in at least two out of the three delineations drawn by the physician. Manual segmentation was employed since tumor and mesorectum were revised with the supervision of the radiologist before segmentation. Once the segmentation has been made the 3D models were processed and tumor volumetries have also been calculated. By applying the Brute Force algorithm, it wascalculated the d_{ij} distance to all the i-th point of the mesorectum volume and the j-th point of the tumor volume. Moreover, we applied a color heat map depicting the shortest distance in red and the further one in blue.

Statistical analysis

CRMs obtained using 3D evaluations were compared to those measured using standard radiology-MRI. Each measure has been repeated trice and blindly by two independent operators. Continuous variables will be analyzed using means and standard deviations and compared using T Test, whereas categorical variables will be analyzed using frequencies and percents. All tests were performed two-tailed and a p value <0.05 was considered as statistically significant. We measured the Interclass Correlation Coefficient (ICC) and the Concordance Correlation Coefficient (CCC) tests using MedCalc Software version 10.2.0.0 (MedCalc Software, MariaKerke, Belgium) in order to test the method performance comparing plain MRI (current clinical gold standard).

Results

Patients

We reviewed 20 patients, 14 males and 6 females (M/F 2.34), with a mean age of 68.3 years, SD 15.1 (range 28-83 years). Tumors' volumetries were calculated using OSIRIX 6.5 (mean tumor's volume 20.55 ± 17.52 cm^3, range 1.25-62.23 cm^3) (8) and 3D imaging segmentation (mean tumor's volume 33.60 ± 22.01 cm^3, range 4.96-91.61 cm^3) reporting a borderline difference between the two methods, T Test 0.052.

3D MRI segmentation and CRM

3D reconstructions were possible in all selected cases and images obtained using the 3D volumes plus the color scale were positive for immediate CRM visualization. Figure 1 shows the results of 3D MRI segmentation using 3DSlicer. Mean CRM obtained using standard radiology was of 1.61 mm (SD 1.89) and the mean CRM calculated using 3D segmentation was of 1.40 mm (SD 1.70), T test p 0.70. Of note, concordance between the 2 methods was of 100.0% if the CRM was positive. Table 1 shows the results of the ICC tests, which was measured in all 20 cases and in patients with negative CRM (>0 mm, 10 patients). Overall, the degree of consistency and the reliability of ratings were optimal with the sole exception of the reliability of single ratings for CRM>0 mm. Table 2 and Figure 2 show the results of the CCC tests: also in this case the correlation and repeatability were optimal considering the overall cases, but lower in the CRM>0 mm sub-group.

Discussion

The assessment of the CRMs remains a key element in defining the clinical and surgical management of rectal cancer patients. Indeed, over the last 2 decades the implementation of the surgical techniques [i.e. the introduction of robotic and laparoscopic surgery (15, 16)], chemotherapy schemes and diagnostic imaging, dramatically changed tumor's management and survival results (17). Even though MRI has been acknowledged as the gold standard technique for the T staging, its implementation is a field of ongoing investigations, with particular respect of the 3D imaging segmentation (2, 18-20). To date, the vast majority of published literature, however, focused on the prediction value of tumor's volumentry and its correlation with the response to neoadjuvant treatment. Indeed a recent review conducted on 14 manuscripts, highlighted that the MRI volumetry assessment of the whole tumor's measurements can be helpful in predicting rectal cancer response and its accuracy in defining ypT0 tumors following chemo-radiation treatments could be up to 80% (21). Furthermore, it has been suggested that 3D imaging is also superior to the standard RACIST criteria for assessing tumor's response (22). On the other hand, our study focused on implementing the definition of the CRMs. Our approach is highly innovative since the 3D volumetry and the application of the color scale can standardize the visualization and the assessment of the minimal distance between tumor and mesorectal fascia. A similar approach has been previously tested only once by another group, even though a different algorithm was applied on a smaller sample of patients, disclosing nevertheless

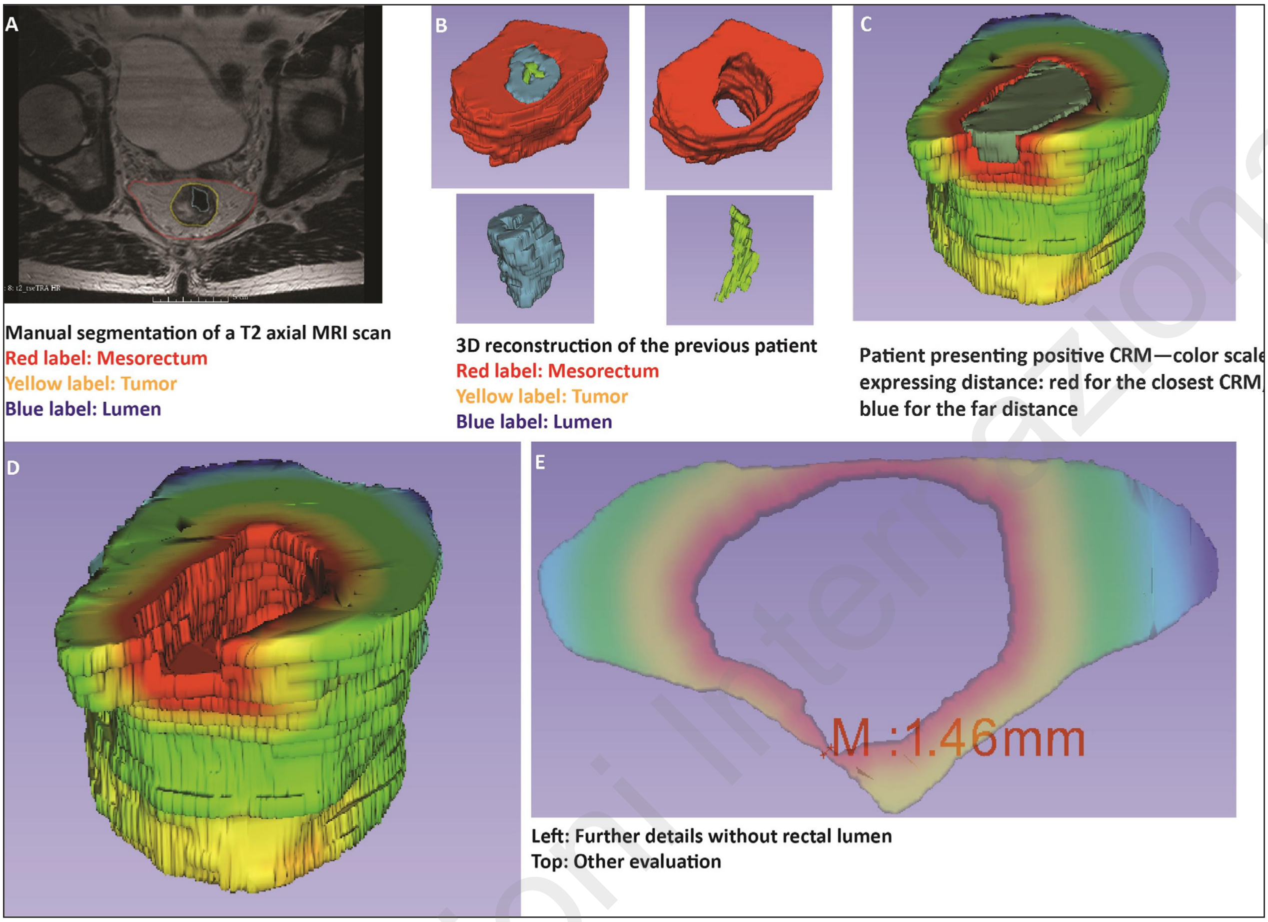

Figure 1 - Results of the 3D MRI imaging segmentation plus application of the color scale: A) Manual segmentation; B) 3D reconstruction of different structures; C) 3D volumes plus color scale; D) 3D mesorectal volume with color scale; E) Example of CRM calculation on the closest red distance.

TABLE 1 - INTERCLASS CORRELATION COEFFICIENT - RESULTS.

	Intraclass correlation [a]	95% Confidence Interval
Overall (20 patients) CRM mean values		
Single measures [b]	**0.8963**	0.7572 to 0.9576
Average measures [c]	**0.9453**	0.8619 to 0.9784
CRM >0 mm (10 patients) CRM mean values		
Single measures [b]	**0.6487**	0.0765 to 0.8995
Average measures [c]	**0.7869**	0.1423 to 0.9471

[a] The degree of consistency among measurements. [b] Estimates the reliability of single ratings. [c] Estimates the reliability of averages of k ratings.

results consistent with the MERCURY method (5). It is our opinion that the method we herein propose could simplified imaging interpretation by the application of the color scale in a 3D volume, thus the closest CRM could be easily visualize. We compared this new method with the gold standard (2D MRI) using the ICC test. The ICC is a test used to assess the consistency, or conformity, of measurements made by multiple observers measuring the same quantity and has been previously used to compare

TABLE 2 - CONCORDANCE CORRELATION COEFFICIENT – RESULTS.

Overall (20 patients) CRM mean values	
Concordance correlation coefficient	**0.8897**
95% Confidence Interval	0.7493 to 0.9536
Pearson ρ (precision)	0.9000
Bias correction factor C_b (accuracy)	0.9886
CRM >0 mm (10 patients) CRM mean values	
Concordance correlation coefficient	**0.6155**
95% Confidence Interval	0.0597 to 0.8800
Pearson ρ (precision)	0.6495
Bias correction factor C_b (accuracy)	0.9478

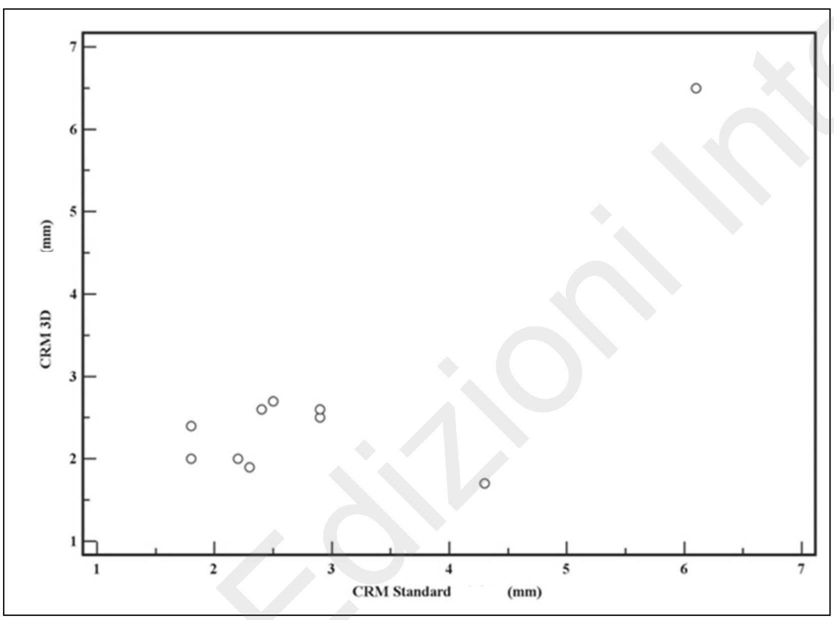

Figure 2 - CCC test: comparison between 3D CRM evaluations *vs* standard MRI imaging.

MRI and 3D evaluations (23, 24). Similarly, these two methodologies were compared using the CCC, which is a coefficient that measures the agreement and the reproducibility between two variables (inter-rater reliability) (25).

Statistical analyses comparing standard radiology, although conducted in a small sample of patients, disclosed that the degree of consistency, the reliability of ratings, the correlation and repeatability were optimal considering the overall cases, but lower in the CRM>0 mm sub-group. These two approaches were 100.0% concordant if the CRM was positive and the statistical comparisons disclosed that the degree of consistency, the reliability of ratings, the correlation and repeatability were optimal considering the overall cases, but lower in the CRM>0 mm sub-group, thus overall, this new method is not inferior comparing standard radiology. In conclusion, the results and the imaging segmentation we obtained were highly promising and could be helpful in defining a standard CRM measurement and suggest that they could also improve clinical practice.

Conflict of interest

None of the Authors has any potential financial conflict of interest related to this manuscript.

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