MR imaging in locally advanced rectal cancer: quantitative evaluation of the complete response to neoadjuvant therapy

Poster No.: C-1405
Congress: ECR 2019
Type: Scientific Exhibit
Authors: C. Tagliaferri, N. Tarallo, M. G. Angeretti, E. Bracchi, G. Xhepa, V. Molinelli, P. Antognoni, R. novario, C. Fugazzola; VARESE/IT
Keywords: Neoplasia, Diagnostic procedure, MR, Oncology, Abdomen
DOI: 10.26044/ecr2019/C-1405

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method ist strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Aims and objectives

Locally advanced rectal cancer (LARC) -defined by the parameters cT3-T4, N -/+, M0- has a 5-year survival rate equal to 50-65%, with a local recurrence rate of 30-40%. Currently the treatment of LARC is oriented towards the use of neoadjuvant therapies, which further reduces the recurrence rate, leading to volume reduction and tumor downstaging. In patients affected by LARC, a complete histopathologic response after CRT occurs in 10-30% of cases at the time of surgery and is related with better prognosis. A "wait and see" approach has been proposed for patients with complete clinical response after CRT. For this reason it is necessary to identify imaging methods capable of discriminating 'complete responders' patients (CR) from "non complete responders" patients (n-CR).
Methods and materials

Fifty patients with MRI diagnosis of LARC between December 2009 and January 2014 were considered for inclusion in our retrospective study based on the following criteria: endoscopic diagnosis and histopathologic (biopsy) proved rectal carcinoma; conventional MR pre-CRT completed with DWI; combined neoadjuvant therapy: the treatment protocol included external beam radiotherapy for a total of 45 to 50.4 Gy (1.8 Gy/fraction) and chemotherapy with 5-fluorouracil (continuous infusion of 225/mg/m²/day for 7 days for the duration of radiation therapy) or Capecitabine per os (825 mg/m² 2 times/day from Monday to Friday for the duration of the radiation treatment); conventional MR completed with DWI after neoadjuvant treatment; histopathological examination of the surgical specimen or, alternatively, biopsy performed during follow-up endoscopy in patients with a strong evidence of complete response to therapy based on clinical and instrumental investigations, in which it was considered preferable an attitude of surveillance to surgical approach.

Of the 50 patients initially enrolled, 18 were excluded: 2 patients for metastatic disease and comorbidities; 1 patient for the poor quality of DWI due to artifacts caused by metallic hip implants; 4 patients lost at follow-up (FU) after performing post-CRT MR; 11 patients underwent surgery after staging MRI. The final population eligible for our study encompassed 32 patients (33 lesions in 32 patients: one patient had two synchronous lesions, one in the rectum and one in the anal canal): 18 males and 14 females - mean age 65.9-years (range: 35-85 years). All MR images were retrospectively evaluated in consensus by two radiologists; the observers were blinded to the clinical patient data and pathology reports.

Twenty-nine of 32 patients underwent TME; 3/32 patients did not undergo surgery, due to strong clinical evidence of a complete response (repeated negative colonoscopy and biopsies after CRT).

Tumour response after CRT was determined in all the 33 lesions according to the pathologic classification suggested by "Dworak's tumor response grading system"

All patients provided written informed consent and were investigated by MRI with a magnetic field of 1.5 Tesla (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany; Philips Achieva, Best, Nederland).Patients did not receive bowel preparation; however, in 57/64 MR examinations rectal distension was performed with 50-120 cc of ultrasound gel; in 7/64 examinations no rectal distension was performed due to lack of cooperation of the patients (4/7 cases) or to low rectal tumors (the lesion was in the lumen of the anal canal in 3/7 cases).

The imaging protocol consisted of the following:
· sagittal TSE T2 weighted (TR: 3.200 ms; TE: 100 ms; FOV 280x280; matrix 348x280; two signal averages slice thickness: 3 mm);

· paraxial (section perpendicular to the longitudinal tumor axis) TSE T2 weighted to accurately evaluate the tumor thickness (TR 3000 ms; TE 100 ms; matrix 348 x 278; three signal averages; FOV 210x228 mm; slice thickness: 3 mm);

· para coronal (section parallel to the longitudinal tumor axis) TSE T2 weighted (TR: 3.200 ms; TE: 100 ms; matrix 348x280; two signal averages; FOV 280x280 mm; slice thickness: 3 mm);

· paraxial DWI (TR: 5.400 ms; TE: 53 ms; matrix: 250x200; four signal averages; FOV: 350x306 mm; slice thickness: 4 mm; using 2 b-value: 0, 800 s/mm²) [5,8,25].

On the T2-weighted images, tumors were defined as areas of intermediate signal compared with the hypointense signal of the normal adjacent muscular rectal wall (Fig. 1a). On post-CRT T2-weighted MR images, areas of markedly low signal intensity (SI) at the location of the primary tumor bed were interpreted as fibrosis. As the risk for residual tumor in these fibrotic areas is known to be about 50%, they were also included in the volumetric measurements (Fig. 1d).

On the pre and post-CRT DW images, measurements were performed on high b-value (800 sec/mm²) images (Fig. 1b,e). During the DWI analysis session, T2-weighted images were used as the reference for tumour location. On DW images tumors were identified as areas of high SI; on the post-CRT acquisition, complete response was defined as complete absence of SI in the previous tumour site, using normal rectal wall as internal reference (Fig. 1e).

Volumetric assessment of the tumor was performed for each lesion, in both paraxial sections on T2-weighted and DW images on high b-value (b= 800 sec / mm²) with identical angled planes. Freehand regions of interest (ROI) were manually drawn at the edges of the tumor for each section containing the lesion. Whole tumor volume was calculated by multiplying each cross-sectional area by the section thickness and then summing all the partial volumes (Fig. 1a,b,d,e).

For both data sets (T2 weighted and DWI), the pre- and post-CRT tumor volumes (V_{T2} and V_{DWI}) were determined; moreover, the tumor volume reduction ratios for both T2-weighted and DW images (#V_{T2}% and #V_{DWI}%) were calculated as follows: (V_{pre} - V_{post})/V_{pre} x 100.

ADC maps were automatically generated by using a monoexponential decay model including the two b values (0 and 800 sec/mm²), on which freehand ROIs were drawn at the edges of the tumor for each axial section containing the lesion (Fig. 1c).
The tumor margins on ADC maps were defined referring to the paraxial T2-weighted and DW images on the high $b$-value ($b = 800 \text{ sec / mm}^2$); mean ADC value was extrapolated by ADC values obtained in the axial sections and the relative standard deviations with the goal of reducing the structural differences induced by the inherent tumor heterogeneity.

When no remaining high SI was visualized on the post-CRT DW images (Fig. 1e), three ROIs were drawn at the former location of the primary tumor with reference to the post-CRT paraxial T2-weighted images (Fig. 1f).

Mean ADC values of the tumor lesions (pre and post-CRT) as well as the percentage of ADC change ($\#\text{ADC\%}$) were calculated. $\#\text{ADC\%}$ was determined as follows: $(\text{ADC}_{\text{post}} - \text{ADC}_{\text{pre}})/\text{ADC}_{\text{pre}} \times 100$. 
Results

Fourteen of the 32 patients included in our study underwent anterior resection of the rectum and 15/32 abdominoperineal resection. Three patients were monitored with endoscopy and concomitant biopsy and underwent FU with MRI investigation every 3-6 months for the first year and then annually.

The mean time between the end of neoadjuvant therapy and restaging MR imaging was 53.4 days (range: 38-82 days) and the mean time between the post-CRT MR imaging and surgery (or biopsy) was 21.2 days (range: 2-60 days).

Pathologic examination revealed 32/33 rectal adenocarcinoma and 1/33 mucinous type adenocarcinoma (32 patients, one with a double synchronous lesion). The histopathological examination provided the following results: 4/33 lesions were considered G0, 13/33 as G1, 7/33 as G2, 2/33 as G3 and 7/33 as G4 (4/7 with histopathological examination of the surgical specimen and 3/7 evaluated on the biopsy material); the CR group is therefore composed of 7/33 patients and the n-CR group of 26/33 patients.

A statistically significant (P <0.0001) reduction of median tumor volume of both $V_{T2}$ and $V_{DWI}$ pre- vs. post-CRT was noted for all 33 lesions included in the study, respectively from 26.4 cm$^3$ to 11.4 cm$^3$ and from 14.8 cm$^3$ to 5.3 cm$^3$ (Table 1).

The pre- and post-CRT median tumor volumes of CR group were significantly lower compared to n-CR group, both on T2-weighted images ($V_{T2pre-CRT}$: 16.1 cm$^3$ vs. 29.97 cm$^3$, P = 0.0037; $V_{T2post-CRT}$: 1.3 cm$^3$ vs. 14.3 cm$^3$, P = 0.001) and on DWI ($V_{DWIpre-CRT}$: 6.6 cm$^3$ vs. 17.99 cm$^3$, P = 0.008; $V_{DWIpost-CRT}$: 0.00 cm$^3$ vs. 8.7 cm$^3$, P = 0.0001) (Table 1). The #V% was significantly higher in CR group compared to n-CR group, both in T2-weighted images (#$V_{T2}$%: 84.9% vs. 50.7%, P = 0.005) and in DWI (#$V_{DWI}$%: 100% vs. 43.7%, P = 0.0001) (Table 1).

For the 33 lesions included in the study a significant increase in median ADC value post- vs. pre-CRT ($1.47 \pm 0.27 \times 10^{-3}$ mm$^2$/sec vs. $1.11 \pm 0.29 \times 10^{-3}$ mm$^2$/sec, P = 0.0001), expressed by the value #ADC% (24.5%), was found.

Nevertheless, no statistically significant difference was found between median ADC values pre-CRT (P = 0.8), post-CRT (P = 0.7) and #ADC% (P = 0.4) in the CR group compared to the n-CR group (Table 1).

The ROC curves were used to compare the diagnostic performances of $V_{T2}$ and #$V_{T2}$%, of $V_{DWI}$ and #$V_{DWI}$%, as well as the ADC values and the #ADC% (Table 2, Fig. 2).
The AUC for the above values pre/post-CRT was respectively 0.86/0.91 for VT2, 0.82/1 for the VDWI and 0.53/0.54 for ADC. A significantly greater accuracy was documented for VT2 and VDWI vs. the ADC values, pre- and post-CRT; nevertheless there were no significant differences in AUC among VT2 and VDWI (Table 2, Fig. 2a,b).

The results for AUC of #VT2% (0.84) and #VDWI% (1) were significantly better than AUC of #ADC% (0.58) (Table 2, Fig. 2c), without statistically significant differences between the #VT2% and #VDWI%.

In the absence of significant differences between VT2 and VDWI, (pre- and post-CRT) and #V%, the more accurate parameters for the assessment of CR (AUC = 1) were represented by the VDWI post-CRT and #VDWI%.

We correctly identified as CR 6/7 lesions on the basis of the absence of SI on DWI on high b-value. One false negative (FN) was documented: on the post-CRT DW images a focal area of high SI at the location of primary tumor was misinterpreted as residual tumor; histopathological examination revealed the complete absence of malignant epithelial cells in the presence of diffuse fibrosis enclosing mucin pools (Fig. 3).

The VDWI post-CRT and #VDWI% of FN were, respectively, 0.5 cm³ and 94.2%; these values hang outward the range of VDWI post-CRT and #VDWI% of n-CR patients (Table 1); moreover, no overlap was found in comparison to the 2/33 lesions of the G3 group (VDWI post: 5.28-21.69 cm³; #VDWI%: 32.5-41.7%).
Fig. 1: Fig. 1-61-year-old woman with distal rectal advanced adenocarcinoma: CR post-CRT. (a) Pre-CRT T2-weighted axial image shows the mass; free hand ROI was drawn along the border of the lesion for calculation of the sectional area of tumor; sectional area was multiplied by section thickness to determine the tumor volume (VT2 = 6.8 cm³). (b) Pre-CRT DW axial image (b value: 800 sec/mm²): a free hand ROI was drawn for the calculation of the sectional area of tumor and of the tumor volume (VDWI = 1.97 cm³). (c) Pre-CRT axial ADC map: a free hand ROI is drawn for the calculation of the ADC; the mean ADC value was calculated from the different axial values (1.23±0.26 x 10⁻³ mm²/sec). (d) Post-CRT T2-weighted axial image shows slight rectal wall thickening with hypointense signal, interpreted as fibrosis; free hand ROI was drawn along the border of the thickening; sectional area was multiplied by section thickness to determine the tumor volume (VT2= 0.94 cm³) and the tumor reduction ratio (#VT2% = 86.2%). (e) Post-CRT DW axial image (b value: 800 sec/mm²): no residual hyperintense signal is observed in the corresponding lesion, therefore tumor volume (VDWI) is equal to 0 cm³ and #VDWI % to 100%. (f) Post-CRT axial ADC map: free hand ROI is drawn along former location of the tumor demonstrated by the T2 weighted image, for the calculation of the ADC (mean value: 1.73 ± 0.19 x 10⁻³ mm²/sec) and ADC change (#ADC% = 41%). A correct prediction of the complete tumor response was made by post-CRT VT2 and VDWI, as
well as by \#VDWI\%. Pathologic examination of resected specimen revealed no residual tumor cells (TRG 4).

**Fig. 2:** Fig. 2-(a) Comparison of the areas under the ROC curves (AUCs) applied to the VT2, VDWI and ADC pre-CRT revealed the absence of a significant difference between the VT2 (0.86) and VDWI (0.82), both with significant difference compared with the ADC (0.53). (b) Comparison of AUCs post-CRT equally revealed the absence of a significant difference between the VT2 (0.91) and VDWI (1), both with significant difference compared with the ADC (0.54). (c) Comparison of AUCs applied to the respective percentage ratios (#VT2\%, #VDWI\% and #ADC\%) revealed absence of a significant difference between the #VT2\% (0.84) and #VDWI\% (1), both with significant difference compared with #ADC\% (0.58). VDWI post-CRT and the #VDWI\% were the most accurate parameters in recognizing the CR (AUC=1).
Fig. 3: Fig. 3-53-year-old man with middle rectal advanced adenocarcinoma CR post-CRT. (a) Pre-CRT T2-weighted axial image shows the tumoral mass bounded by free hand ROI (VT2 = 9.9 cm³). (b) Pre-CRT DW axial image (b value: 800 sec/mm²) shows an hyperintense signal in the tumoral area bounded by the free hand ROI (VDWI = 8.6 cm³). (c) Post-CRT T2-weighted axial MR image shows rectal wall thickening with an area of intermediate SI interpreted as residual tumor, bounded by the free hand ROI (VT2 = 0.9 cm³). (d) Post-CRT axial DWI shows a linear hyperintense signal, interpreted as residual tumor at qualitative evaluation, bounded by the ROI (VDWI = 0.5 cm³). Although both T2 weighted and DW images wrongly demonstrate a residual tumor, a correct prediction of the complete tumor response is made by post-CRT VT2 and VDWI as well as by #VT2% (94%) and #VDWI% (94.2%). Pathologic examination of resected specimen revealed no residual tumor cells (TRG 4).

© RADIOLOGIA, UNINSUBRIA, FONDAZIONE CIRCOLO MACCHI - VARESE/IT
Conclusion

Conventional MR sequences are not sufficiently reliable in distinguishing between residual tumor and post-CRT tissue fibrosis. However, it has been shown that the qualitative assessment of DWI sequences significantly improves the diagnostic performance of conventional MRI in the evaluation of tumor response to CRT: particularly, in distinguishing between CR and n-CR patients, DWI has shown a higher sensitivity (52-64% vs. 0-40%) and an almost comparable specificity (89-97% vs. 92-98%) vs. standard MR sequences.

However, DW images have limitations, as complete tumor regression is not always accompanied by absence of SI, since diffuse fibrosis associated with chronic inflammation, the presence of mucin pools, the air-rectal wall interface or the collapsed rectal wall may be visualized as high SI, making difficult the identification of CR: this also occurred in 1/7 CR patients of our series (Fig. 3).

Therefore, the MR quantitative evaluations have been proposed by calculating the mean ADC values, the conventional volumetry on T2 weighted images ($V_{T2}$) and, the volume measured on the DW images ($V_{DWI}$), as well as the ratio between the values before and after CRT ($\#\%$). In our series, considering the entire group of lesions (CR + n-CR), the post-CRT ADC value, while being significantly higher than the pre-CRT ADC value, was not able to distinguish CR patients from n-CR; moreover the $\#ADC\%$ was not able to make such discrimination. Similar conclusions on the limited usefulness of the various measurements of the ADC- including the $\#ADC\%$ - for the assessment of CR also emerged from other studies.

Concerning the volumetric evaluation with MR T2-weighted imaging, some studies associate with a volume reduction; other studies did not find any significant difference in order to identify the CR (TRG 4) as well as the "good responders" (TRG 3-4).

Other studies, published between 2011 and 2015 have argued that the tumor volume measured in the DW images was more accurate than that obtained in the conventional T2 MR sequences. The results of our series reveal a good accuracy of post-CRT $V_{T2}$(AUC = 0.91) and the $\#V_{T2}\%$ (AUC = 0.84) (Table 2; Fig. 2); the post-CRT $V_{DWI}$ and $\#V_{DWI}\%$ resulted more accurate (AUC = 1) compared to the corresponding post-CRT $V_{T2}$ and $\#V_{T2}\%$; however, the differences were not statistically significant.

Therefore, our experience confirms that volumetry on DW images is more accurate than that on T2 weighted images: in particular, post-CRT $V_{DWI}\# 0.5 \text{ cm}^3$ and $\#V_{DWI}\% \# 83%$(our values of optimal cut-off) could indicate a pathologic complete response. However, it still remains difficult to differentiate between patients with a CR (TRG 4) and patients with small microscopic clusters of residual neoplasm (TRG 3); further studies are required to address this issue.
Nevertheless at present, although the tumor volumes determined on the basis of the presence (or absence) of high-signal intensity areas on DW-MRI better represent the existence of residual viable tumor, we can hypothesize - in agreement with Curvo-Semedo - that a visual evaluation of a high-signal intensity area suggestive of residual tumor is sufficient, and volumetric measurements are not even required.

Moreover, the combination of MRI with clinical assessment (digital rectal examination and endoscopy) is recommended as the optional strategy for a safe and accurate selection of CRs after CRT.

There were some limitations to our study: the small number of selected patients; the small size of the pre-CRT lesions with pathologic complete response; histopathological evaluation of tumor regression to therapy was performed on biopsy in 3/7 CR; the lack of direct correlation between volumetric data obtained by MR images and the volumetric data provided by the surgical specimens; the possible errors in the positioning and size of the ROIs drawn on the tumor margins; the inter-observer reproducibility of the method was not evaluated because of the long time required for measurements of volumes and ADC values; finally, post-CRT N parameter, so far considered in a single study, was not assessed. However, the prevalence of a positive lymph node status in case of CR of the primary tumor after CRT is very low (8%); moreover, standard MRI is rather accurate in lymph node staging after CRT, so the addition of functional imaging, such as DWI, may not even be necessary.

In conclusion, DW images improve the results of standard follow-up MR protocols in order to identify CR patients after neoadjuvant CRT in patients affected by LARC. The functional volumetry is better than the conventional volume, although no statistically significant differences were detected in this study. In particular, both post-CRT V\textsubscript{DWI} and \#V\textsubscript{DWI}\% results are very accurate; however standardized cut-off values are not available. Conversely, the pre- and post-CRT ADC values and #ADC\% are not sufficiently reliable to distinguish the CR patients from the total group of n-CR patients.
References

1.

2.

3.

4.