European Journal of Surgical Oncology 45 (2019) 347–352

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Diffusion-weighted imaging and loco-regional N staging of patients with colorectal liver metastases

Cristiana Bonifacio [a, 1], Luca Viganò [b, 1], Paolo Felisaz [a], Egesta Lopci [c], Matteo Cimino [b], Dario Poretti [a], Matteo Donadon [b], Vittorio Pedicini [a], Fabio Procopio [b], Arturo Chiti [c], Luca Balzarini [a], Guido Torzilli [b, *]

[a] Dept. of Radiology, Humanitas Clinical and Research Center, Humanitas University, Rozzano, Milan, Italy
[b] Division of Hepatobiliary and General Surgery, Department of Surgery, Humanitas Clinical and Research Center, Humanitas University, Rozzano, Milan, Italy
[c] Dept. of Nuclear Medicine, Humanitas Clinical and Research Center, Humanitas University, Rozzano, Milan, Italy

ARTICLE INFO

Article history:
Received 26 May 2018
Received in revised form
19 November 2018
Accepted 23 November 2018
Available online 28 November 2018

Keywords:
Colorectal liver metastases
Lymph node metastases
Diffusion-weighted MRI
Staging of colorectal tumors
N staging
ADC measurement

ABSTRACT

Introduction: Diffusion-weighted MRI (DWI) contributes to N staging of rectal cancers and diagnosis of colorectal liver metastases (CLM). About 15% of CLM patients have loco-regional lymph node (LN) metastases that impact prognosis and treatment strategy. This retrospective study is the first one to evaluate quantitative ADC measurement as a tool to identify metastatic LNs in patients with liver metastases from colorectal cancer.

Methods: All consecutive patients undergoing surgery for CLM between 2008 and 2015 were considered. Inclusion criteria were: intraoperative retrieval of at least one LN; LN $\geq$ 5 mm; DWI performed $\leq$2 months before surgery. The ADC and ADC_{ratio} (ADC_{LN}/ADC_{CLM}) were computed by two radiologists for all the LNs.

Results: Among 555 patients operated for CLM, 32 met the inclusion criteria. Fifty-six LNs were analyzed and 28 were metastatic. ADC and ADC_{ratio} in metastatic LNs were lower than in benign LNs (ADC = 1.37 vs. 1.83 $\times$ 10^{-3} mm^2/s, $p < 0.001$; ADC_{ratio} = 1.26 vs. 1.73, $p < 0.001$). The optimal cut-off value for ADC was 1.48 x 10^{-3} mm^2/s (AUC = 0.85, $p < 0.001$, sensitivity/specificity/accuracy 79%/93%/86% in per LN-analysis and 94%/86%/91% in per-patient analysis). The optimal cut-off for ADC_{ratio} was 1.15 (AUC = 0.80, $p < 0.001$, sensitivity/specificity/accuracy 69%/93%/81% and 76%,93%/84%). Excellent inter- and intra-operators' agreements were observed.

Conclusion: In patients with CLM, ADC values < 1.48 x 10^{-3} mm^2/s can be postulated as a cut-off to distinguish metastatic LNs.

Introduction

Colorectal carcinoma (CRC) is one of the most common tumors affecting western countries, with a lifetime incidence of 6% and an overall survival rate of 40–60% at 5 years, staging dependent [1]. Among patients with CRC, more than 50% have colorectal liver metastases (CLM) at diagnosis (synchronous disease) or will develop it during the follow-up (metachronous) [2]. Liver surgery in combination with perioperative chemotherapy is their standard treatment and, to date, is indicated whenever a complete resection with adequate residual liver parenchyma is feasible [3–5]. The presence of extrahepatic disease simultaneous with CLM is a negative prognostic factor but is not a contraindication to surgery [6]. Lymph-node (LN) metastases deserve some additional considerations. The surgical indication depends on the site of metastatic LNs: if metastases are confined to the hepatic pedicle (about 10–15% of patients) resection is indicated; if they are extended to the celiac or retropancreatic area the benefits from surgery are doubtful; in presence of inter-aorto-caval LN metastases surgery is contraindicated [7,8].

Magnetic resonance imaging (MRI) is the present gold standard for the local staging of rectal cancers (T staging) [9] and is very

* Corresponding author. Department of Surgery, Division of Hepatobiliary & General Surgery, Humanitas Clinical and Research Center - IRCCS, Humanitas University, Via Manzoni 56, 20089, Rozzano, Milan, Italy.
E-mail address: guido.torzilli@hunimed.eu (G. Torzilli).
[1] Bonifacio C and Viganò L equally contributed to the manuscript.

https://doi.org/10.1016/j.ejso.2018.11.018
0748-7983/

accurate in the detection of liver metastases (M staging), with 80%–88% sensitivity and 93–97% specificity [10]. The nodal staging remains the major drawback of MRI, with an accuracy ranging from 62% to 85% [11]. Since the main parameter to assess LN status is size, the morphological imaging modalities (computed tomography and MRI) have reduced diagnostic precision in the assessment of upper abdomen LN stations where benign nodes $\geq$10 mm are common. Positron emission tomography with fluorodeoxyglucose (FDG-PET) is more accurate since it depends on metabolic activity rather than morphology, but has limited reliability in small LNs evaluation [12].

Diffusion-weighted magnetic resonance imaging (DW – MRI or DWI) is a recently introduced modality based on the Brownian motion of water molecules. Free water displacement is consistent with a drop of signal in the DWI image and an increase of the apparent diffusion coefficient (ADC); on the contrary, water restriction due to high tissue cellularity and fibrous stroma, typical features of neoplasms, increases the signal in the DWI image and reduces the ADC [13]. DWI is more sensitive and accurate than conventional MRI for the detection of liver metastases [14] and is useful to characterize liver lesion [15]. Considering LNs, DWI has been proposed for the N staging of gastric carcinomas [16], endometrial cancers [17], breast cancers [18,19] and head and neck cancers [20,21] with promising results. Only some of these studies have evaluated DWI with quantitative measurement of ADC with ambiguous and sometimes contradicting results [22]. To date, there are no available studies assessing the role of DWI in the detection of locoregional LN metastases of CLM.

The aim of the present study was to elucidate the contribution of DWI with ADC measurement to the N staging of CLM, a completely unexplored issue.

Methods

The Institutional Review Board of our hospital approved this retrospective study and the requirement of informed consent was waived. All patients undergoing surgery for CLM from January 2008 to December 2015 at the author's institution were considered. The retrospective research was performed on 555 patients and inclusion criteria were as follows:

1) intraoperative retrieval of at least one LN in one of the following stations classified according the "Japanese classification for Gastric Cancer" [23]: hepatic pedicle (stations 12a, b, and p), common hepatic artery (station 8), celiac trunk (station 9), retropancreatic area (station 13), lesser gastric curvature (station 3), paraortic (station 16);
2) a minimal LN size of 5 mm;
3) availability of an MRI examination with DWI performed $\leq$2 months before surgery.

Overall, 34 patients fulfilled the inclusion criteria. Two patients had low-quality MRI studies (excessive artifacts in the DWI) and were excluded. Finally, 32 patients were included in this study.

Imaging protocol

MRI examinations were performed with 1,5 or 3 tesla (T) scanners (Magnetom Symphony or Verio, Siemens AG, Erlangen, Germany), with phased array coils. The protocol included T2 axial and coronal sequences, T1 axial breath-hold in-phase and opposed-phase sequences, dynamic contrast-enhanced axial sequences at 0, 35, 90, 120 and 240 s and late acquisitions with liver-specific contrast medium, obtained after 20 min for Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany) and after 90 min for Gd-DTPA (MultiHance, Bracco Imaging SpA, Milan, Italy). Diffusion-weighted images were acquired in free breathing in the axial plane, always including at least the whole liver and the kidneys. The following parameters were used for DWI: inversion recovery spin echo, echo planar imaging, TR 11500 ms, TE 73 ms, TI 180 ms (1,5 T) or 201 ms (3 T), slice thickness 6 mm, averages 6, b values: 0, 50, 650, 1000, diffusion directions 3.

Preoperative patient management and surgical procedures

The preoperative management of patients with CLM has been previously reported [24,25]. In brief, standard preoperative staging included thoracoabdominal CT, hepatic MRI, and PET-CT. Only patients amenable to complete resection were considered for surgery. A multidisciplinary tumor board discussed the management of every patient. The preoperative diagnosis of metastatic LN was managed according to their site, as follows: patients with LN metastases confined to the hepatic pedicle (station 12) were candidate to surgery after preoperative chemotherapy; patients with LN metastases in the celiac and/or retropancreatic area (stations 8, 9, and 13) were discussed on a case-by-case basis and candidate to surgery in few cases after a good response to chemotherapy; patients with LN metastases in other stations (3 or 16) were usually excluded from surgery independently from their response to chemotherapy. Patients undergoing preoperative chemotherapy were restaged after treatment (4–6 cycles) and surgery was scheduled in case of tumor response or stabilization.

The surgical technique for patients with CLM was previously reported [26]. Specifically considering the LN status, two scenarios were possible. First, patients with preoperative diagnosis of LN metastases. In this scenario, paraortic LNs were systematically sampled after laparotomy and sent to the pathologist for the frozen section: if LNs were metastatic, the planned surgical procedure was canceled; if not, the liver resection was performed together with a LN dissection of the hepatic pedicle, the celiac and the retropancreatic area. Second, patients with intraoperative suspicion of metastatic LN (N0 at preoperative imaging). The suspected LN was systematically sampled and sent to the pathologist for the frozen section: if positive, the authors adopted the same policy of the first scenario; if negative, the liver resection was performed without LN dissection.

During the LN dissection, every single LN station (12a, 12p, 12b, 8, 9, and 13) was separately sent to the pathologist for the final examination.

Imaging analysis

Two radiologists blinded to the final pathology reports reviewed the abdominal MRI examinations focusing on the LN station removed at surgery (CB with a 13-year experience and PF with a one-year experience in abdominal MRI). The LN size was measured as the longest LN diameter on transaxial T2-weighted images. The software Intellispace Portal (Philips Healthcare, Amsterdam, The Netherlands) was used to analyze the DWI trace images and to calculate the ADC maps, obtained using all the b-values. Only LNs univocally referable to those depicted by the surgical report were analyzed. The selection was based on the anatomical localization of the nodes, as described in "Japanese classification for Gastric Cancer". LNs were identified at anatomical sequences and a circular region of interest (ROI) with a diameter between 15 and 20 mm^2 was placed at the center of the selected LN in order to obtain an ADC value. The first measure obtained by the software was recorded. ADC values of one liver metastasis were also collected in order to calculate the ratio ADC node/ADC liver metastasis (ADC_{ratio}). In case of necrotic lesion, the ROI was placed within the solid

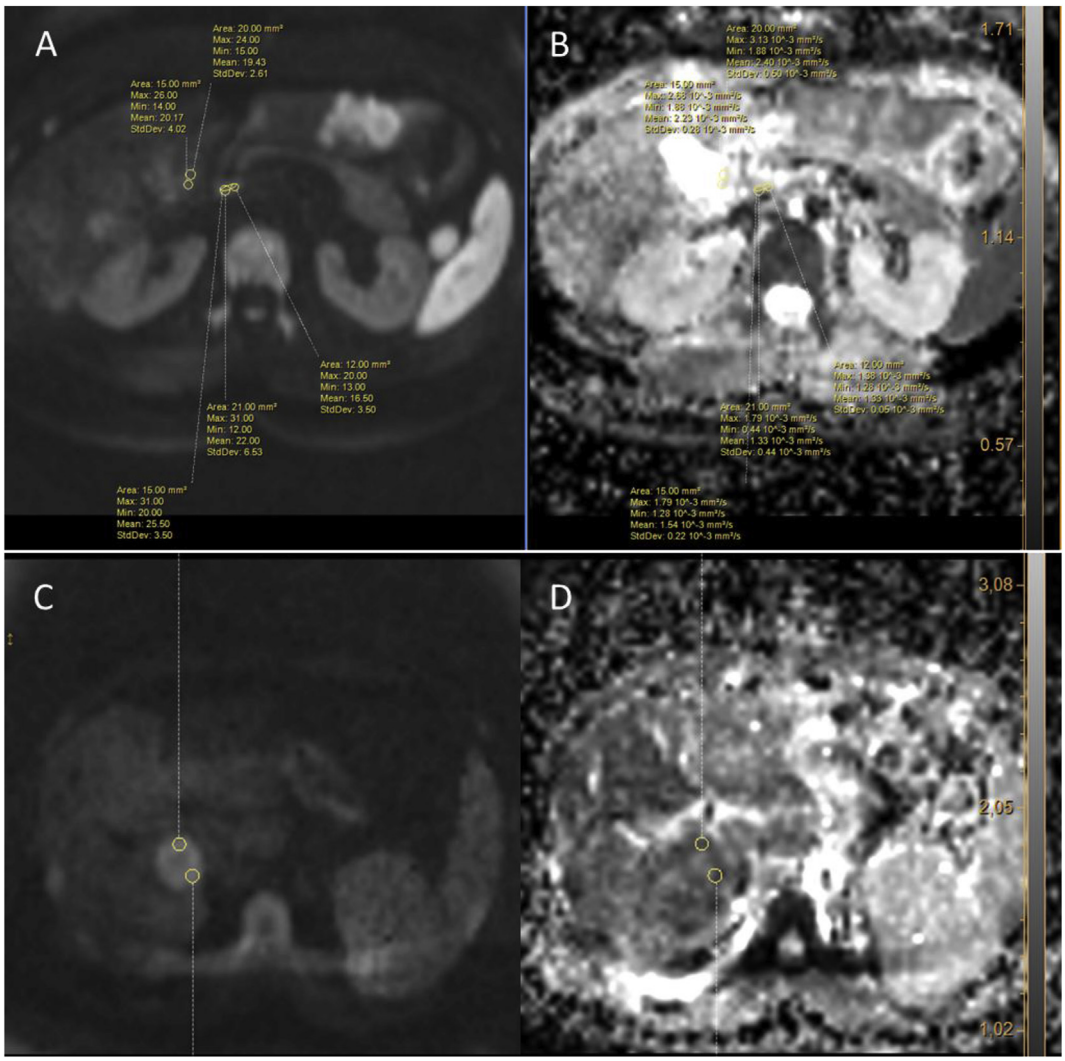

Fig. 1. Examples of ADC measurements in the DWI and ADC maps images. **A-B.** Measurement of nodes in the hepatic pedicle and retropancreatic area (stations number 12 and 13 according to the "Japanese classification for Gastric Cancer" [23]). On the left the trace image with low B0 is used to place the ROI of 15–20 mm^2 diameter in the center of the node, the software automatically matches the ROI in the ADC maps (right) and the measure of ADC is recorded. **C-D.** A measure of ADC taken in a liver metastasis. The ROI is placed on the rim of the node with the aim to avoid the liquefied central part of the lesion.

component. Fig. 1 is an example of measurement of ADC value in hepatic pedicle and retropancreatic LNs.

Statistical analysis

All statistical analyses were performed with MedCalc (MedCalc Software, Ostend, Belgium). Gaussian distribution of the continuous variables was assessed graphically and parametric (unpaired *t*-test) or nonparametric tests (Mann-Whitney *U* test) were used accordingly. Receiver Operating Characteristic (ROC) curves were plotted to identify the best cut-off of ADC and ADC_{ratio} for LN metastases prediction. Then we calculated the number of true-positive, true-negative, false-positive and false-negative with respect to our reference standard (histology). Sensitivity, specificity, negative and positive predictive values (NPV and PPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and accuracy were computed. Finally, the Bland-Altman analysis with 95% limits of agreement was used to assess inter and intra-operators' agreements. P values < 0.05 were considered statistically significant for all the analyses.

Results

A total of 32 patients (18 males, 14 females, mean age 60 ± 11.8, range 35–79) undergoing liver resection for CLM and simultaneous regional LN dissection were analyzed. Seventeen patients had LN metastases (53.1%). Patients' characteristics are summarized in Table 1.

LN data

Overall, 56 LNs >5 mm were retrieved, 28 (50%) of which were metastatic. The mean diameter of malignant and benign LNs was similar (15 ± 10 mm, range 6–45 vs. 15 ± 6 mm, range 6–40, $p = 0.954$). LN size was not a reliable criterion to distinguish malignant and benign LNs (accuracy 50% if a cut-off of 10 mm was used; 52% if a cut-off of 20 mm was used). LN sites are summarized in Table 1, being the pedicle and the common hepatic artery the commonest (22 and 16, respectively).

Table 1
Patient characteristics and lymph node status. Lymph node stations are classified according to the "Japanese classification for Gastric Cancer" [23].

	n (%)	
Patient characteristics		
Age >70 years	9 (28.1)	
Male sex	18 (56.3)	
Primary tumor		
Rectal cancer	6 (18.8)	
T3-4	25/28 (89.3)	
N+	23/28 (82.1)	
Liver metastases		
Synchronous	18 (56.3)	
Bilobar metastases	18 (56.3)	
Number of nodules, median	4 (1–32)	
>3	17 (53.1)	
>10	6 (18.8)	
Largest diameter >50 mm	9 (28.1)	
CEA>200 ng/mL	1 (3.1)	
Preoperative chemotherapy	21 (65.6)	
Lymph node stations		
Status	N+	N-
Overall	28	28
3 (lesser curvature)	2	2
8 (common hepatic artery)	9	7
9 (celiac trunk)	3	0
12 (hepatic pedicle)	8	14
13 (retropancreatic head)	4	4
16 (paraortic)	3	0

Table 2
Mean diameter, ADC and ADC_{ratio} values of the malignant and the benign nodes.

	N+	N-	p
Diameter (mm)	15 ± 10	15 ± 6	0.954
ADC (x 10^{-3} mm^2/s)	1.37 ± 0.41	1.83 ± 0.37	<0.001
ADC_{ratio}	1.26 ± 0.58	1.73 ± 0.43	<0.001

LN and DWI

Mean ADC value of the malignant LNs was 1.37×10^{-3} $mm^2/s \pm 0.41$ while mean ADC of the benign ones was 1.83×10^{-3} $mm^2/s \pm 0.37$ ($p < 0.001$). ADC_{ratio} of the malignant LNs was also significantly lower than that of benign ones (1.26 ± 0.58 vs. 1.73 ± 0.43, $p < 0.001$) (Table 2). The difference of ADC values between the benign and the malignant LNs was independent from the LN size (Table 3). ADC_{ratio} of the malignant LNs was also lower than that of the benign ones for all LNs size (≤10, 10–20, and ≥20 mm), but the difference was less pronounced in LNs larger than 20 mm (Table 3).

Table 3
Mean ADC and ADC_{ratio} values of the benign and the malignant nodes according to their size.

Lymph node size	ADC (x 10^{-3} mm^2/s)		p	ADC_{ratio}		p
	N+	N-		N+	N-	
≤10 mm	1.33	1.61	<0.001	1.10	1.66	0.006
10–20 mm	1.21	1.95	<0.001	1.40	1.85	0.002
≥20 mm	1.38	1.88	0.092	1.35	1.65	0.203

In a per-LN analysis, ROC curve analysis for the ADC values showed an area under the curve (AUC) of 0.85, $p < 0.001$. The optimal cut-off value for ADC was 1.48 x 10^{-3} mm^2/s with a sensitivity of 79% and a specificity of 93%. (Fig. 2a). For the ADC_{ratio}, the AUC was 0.80 ($p < 0.001$). The optimal cut-off value for the ADC_{ratio} was 1.15 with a sensitivity of 69% and a specificity of 93% (Fig. 2b).

In a per-patient analysis, the ADC cut-off value of 1.48 had a sensitivity of 94% and a specificity of 86%. ADC_{ratio} of 1.15 had a sensitivity of 76% and a specificity of 93%.

Twenty-one patients (36 LNs) had preoperative chemotherapy, including 9 patients (14 LNs) receiving less than 6 cycles of chemotherapy and 12 patients (22 LNs) receiving 6 cycles or more. The median ADC value in the malignant LNs progressively increased in the three groups (1.16 x 10^{-3} mm^2/s if no chemotherapy, 1.21 x 10^{-3} mm^2/s if < 6 cycles, and 1.39 x 10^{-3} mm^2/s if ≥ 6 cycles), but in all groups the malignant LNs had lower ADC values than the benign LNs (ADC values in benign LNs were 1.86 x 10^{-3} mm^2/s if no chemotherapy, 1.66 x 10^{-3} mm^2/s if < 6 cycles, and 1.63 x 10^{-3} mm^2/s if ≥ 6 cycles, respectively). ADC cut-off value of 1.48 x 10^{-3} mm^2/s had a sensitivity, specificity and accuracy of 100%, 90%, and 95% in patients without preoperative chemotherapy; 100%, 86%, and 93% in patients receiving less than 6 cycles of chemotherapy; and 64%, 100%, and 82% in patients receiving 6 cycles or more of chemotherapy.

In the present series, 19 LNs in 12 patients were removed because of an intraoperative suspicion of metastasis. Twelve of 19 LNs were malignant, and all but one had an ADC value < 1.48 x 10^{-3} mm^2/s. On the opposite, all the 7 LNs removed for suspicion of metastasis but benign at final pathology had an ADC value > 1.5 x 10^{-3} mm^2/s. Accordingly, the ADC cut-off value of 1.48 x 10^{-3} mm^2/s would have correctly classified all but one LNs.

The Bland-Altman method applied to ADC measurements demonstrated an intra-individual mean difference of 0.02 (limits of agreement −0.30 to 0.33) and an inter-individual mean difference of −0.02 (limits of agreement −0.42 to 0.38); both the mean

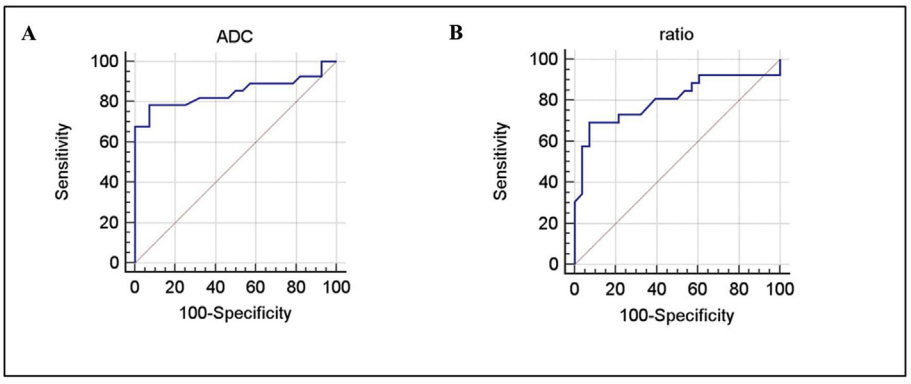

Fig. 2. Receiver Operator Characteristic (ROC) curves demonstrating the diagnostic performance of ADC and ADC_{ratio}. for detecting metastatic lymph nodes. **A.** ROC curve of the absolute values of ADC. Area under the curve (AUC) 0.85 C.I. 0.73 to 0.93 $p < 0.001$. **B.** ROC curve of the values of ADC_{ratio}. AUC 0.80 C.I. 0.67 to 0.90 $p < 0.001$.

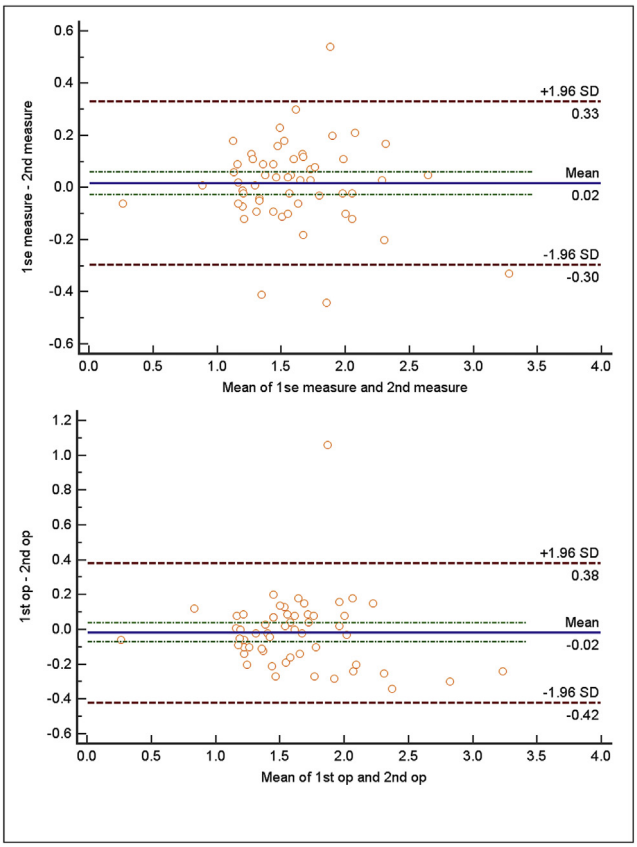

Fig. 3. Bland-Altman plots for the intra- and inter-observer agreements. In the first graph, the difference of the ADC values observed by the first operator is plotted on the y-axis against their mean on the x-axis. In the analogous second graph, the difference of the ADC values observed by the first and the second operator is plotted against their mean. The continuous line represents the mean absolute difference of the observations (bias). The dashed lines represent the limits of agreement (+/-1.96 SD of the mean difference). The bias is not significant because the line of equality is within the confidence interval of the mean difference (dotted lines).

differences of the measurements fell within their confidence interval, consisting with not significant differences and not significant bias between the measurements (Fig. 3).

Discussion

The present study is the first one to assess the role of DWI in detecting metastatic LNs in patients with CLM. We found a straightforward reduction of the ADC and ADC_{ratio} values in metastatic LNs compared to non-metastatic LNs. Evaluating each of the LNs as a distinct outcome (per-LN analysis), the accuracy was 86% for ADC (cut-off 1.48×10^{-3} mm^2/s) and 81% for ADC_{ratio} (cut-off 1.15). Considering the individuals as an outcome, being N+ or N- (per-patient analysis), the tests were even more accurate (91% and 84% for ADC and ADC_{ratio}, respectively). The size of LN did not impact ADC values, while prolonged chemotherapy slightly impaired performances of DWI.

The contribution of DWI to N staging was mainly analyzed for rectal cancers, but with controversial results. Yasoui et al. [27], in a limited series of 46 consecutive patients, found a reduction in ADC and ADC_{ratio} values in metastatic LNs with an accuracy of 75% (cut-off 1.44×10^{-3} mm^2/s) and of 79% (cut-off 1.46), respectively. Cho et al. [28], in a study on 34 patients, demonstrated lower ADC values in metastatic LNs with an accuracy of 72% (cut-off of 1.0×10^{-3} mm^2/s). Heijnen et al. [29], in another small series of 21 patients, did not find a statistical difference in ADC values between normal and malignant mesorectal LNs, though they used a clear-cut lesion-by-lesion matching, mapping the nodes in anatomical specimens and comparing them with the relative MRI image. Lambregts et al. [30], previously found different results in a limited series of 30 patients affected by advanced rectal cancer. Authors underlined that preoperative chemo-radiation may result in nodal necrosis and a paradoxical increase in the ADC values (due to increased diffusivity in a liquefied tissue). The problem is not trivial, because many patients affected by CLM are treated with chemotherapy before surgery. In the present series, two-third of patients had preoperative chemotherapy. ADC performances were not altered after a short chemotherapy (<6 cycles, accuracy 93%), while they were slightly impaired after a prolonged treatment (≥6 cycles, accuracy 82%).

To the best of our knowledge, this is the first study on upper abdominal LN stations in CLM. In expert consensus statements about CLM, the contribution of DWI to N staging has never been considered [5,31]. The absolute ADC value achieved good performances in LN metastases detection, better than the ADC_{ratio}. Of note, we identified the same cut-off reported by Yasoui et al. [27] for mesorectal LNs. The proposed ADC cut-off value had an accuracy of 86% and correctly classified all but one LNs removed because of an intraoperative suspicion of metastasis. In two studies on mesorectal LNs, the ADC_{ratio} performed better than the absolute ADC [27,29]. The ADC_{ratio} is a normalized parameter that relates the ADC of a LN to the ADC of the primary neoplasm and should be able to reduce inter-subject variability. Our study was focused on patients with liver metastases and therefore the reference for the ADC_{ratio} was chosen among liver metastases. This choice is flawed by several limitations, the major being related to the fact that CLMs have major modifications after preoperative chemotherapy, including the presence of some necrotic parts that may lead to an overestimation of the metastases ADC.

The present study has some significant drawbacks, the majors being its retrospective design and that it is based on a small series of consecutive patients. These limitations are amplified by the fact that patients were studied on two different MRI scanners, using different protocols. Moreover a minimum LN size was required for the analysis (diameter at least of 5 mm), therefore approximately half of the total amount of LNs with histologic diagnosis were excluded. Second, the ROI was placed on a single slice, but it is well known that tissues can be heterogeneous in terms of their internal structure and signal intensity. Especially for LNs in the upper abdominal stations, with a mean size of 15 mm, a volumetric ROI might have been more appropriate [22]. Nevertheless, the greater mean size of the LNs of our population, compared to the mesorectal nodes (mean size 6 mm) [28], facilitated our measurements and might be one of the reasons of the better accuracy we found, compared to the previous studies. Further, in the present study ADC values were not associated with LN size. As a final remark, the influence of chemotherapy before surgery must be carefully taken in consideration when considering the clinical value of DWI in patients affected by CLM.

Conclusions

We found significant differences in ADC and ADC_{ratio} values between metastatic and benign LNs, supporting the commonly described relationship that relates malignancy with reduction of diffusivity. DWI performances were even better than those previously reported for mesorectal LNs. In patients with CLM, locoregional LNs with ADC values < 1.48 x 10^{-3} mm^2/s should be considered as metastatic. Our report stands among others based on small retrospective series of patients. Although the perspective

of DWI in assessment of LNs in colorectal cancers is promising, a prospective clinical trial able to generate robust data is warranted.

References

[1] Kekelidze M, D'Errico L, Pansini M, Tyndall A, Hohmann J. Colorectal cancer: current imaging methods and future perspectives for the diagnosis, staging and therapeutic response evaluation. World J Gastroenterol 2013;19:8502–14. https://doi.org/10.3748/wjg.v19.i46.8502.

[2] Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254–9. https://doi.org/10.1097/01.sla.0000217629.94941.cf.

[3] Vigano L, Capussotti L, Majno P, Toso C, Ferrero A, De Rosa G, et al. Liver resection in patients with eight or more colorectal liver metastases. Br J Surg 2015;102:92–101. https://doi.org/10.1002/bjs.9680.

[4] Vauthey JN, Choti MA, Helton WS. AHPBA/SSO/SSAT Consensus Conference on hepatic colorectal metastases: rationale and overview of the conference. January 25 Ann Surg Oncol 2006;13:1259–60. https://doi.org/10.1245/s10434-006-9017-9. 2006.

[5] Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncol 2012;17:1225–39. https://doi.org/10.1634/theoncologist.2012-0121.

[6] Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. Lancet Oncol 2009;10:801–9. https://doi.org/10.1016/S1470-2045(09)70081-6.

[7] Jaeck D, Nakano H, Bachellier P, Inoue K, Weber JC, Oussoultzoglou E, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. Ann Surg Oncol 2002;9:430–8. http://www.ncbi.nlm.nih.gov/pubmed/12052752.

[8] Adam R, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol 2008;26:3672–80. https://doi.org/10.1200/JCO.2007.15.7297.

[9] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012;23:2479–516. https://doi.org/10.1093/annonc/mds236.

[10] Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674–84. https://doi.org/10.1148/radiol.10100729.

[11] Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging–a meta-analysis. Radiology 2004;232:773–83. https://doi.org/10.1148/radiol.2323031368.

[12] Tsunoda Y, Ito M, Fujii H, Kuwano H, Saito N. Preoperative diagnosis of lymph node metastases of colorectal cancer by FDG-PET/CT. Jpn J Clin Oncol 2008;38:347–53. https://doi.org/10.1093/jjco/hyn032.

[13] Qayyum A. Diffusion-weighted imaging in the abdomen and pelvis: concepts and applications. Radiographics 2009;29:1797–810. https://doi.org/10.1148/rg.296095521.

[14] Parikh T, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS, et al. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. Radiology 2008;246:812–22. https://doi.org/10.1148/radiol.2463070432.

[15] Namimoto T, Yamashita Y, Sumi S, Tang Y, Takahashi M. Focal liver masses: characterization with diffusion-weighted echo-planar MR imaging. Radiology 1997;204:739–44. https://doi.org/10.1148/radiology.204.3.9280252.

[16] Cheng J, Wang Y, Deng J, McCarthy RJ, Wang G, Wang H, et al. Discrimination of metastatic lymph nodes in patients with gastric carcinoma using diffusion-weighted imaging. J Magn Reson Imag 2013;37:1436–44. https://doi.org/10.1002/jmri.23925.

[17] Rechichi G, Galimberti S, Oriani M, Perego P, Valsecchi MG, Sironi S. ADC maps in the prediction of pelvic lymph nodal metastatic regions in endometrial cancer. Eur Radiol 2013;23:65–74. https://doi.org/10.1007/s00330-012-2575-2.

[18] Luo N, Su D, Jin G, Liu L, Zhu X, Xie D, et al. Apparent diffusion coefficient ratio between axillary lymph node with primary tumor to detect nodal metastasis in breast cancer patients. J Magn Reson Imag 2013;38:824–8. https://doi.org/10.1002/jmri.24031.

[19] Fornasa F, Nesoti MV, Bovo C, Bonavina MG. Diffusion-weighted magnetic resonance imaging in the characterization of axillary lymph nodes in patients with breast cancer. J Magn Reson Imag 2012;36:858–64. https://doi.org/10.1002/jmri.23706.

[20] de Bondt RB, Hoeberigs MC, Nelemans PJ, Deserno WM, Peutz-Kootstra C, Kremer B, et al. Diagnostic accuracy and additional value of diffusion-weighted imaging for discrimination of malignant cervical lymph nodes in head and neck squamous cell carcinoma. Neuroradiology 2009;51:183–92. https://doi.org/10.1007/s00234-008-0487-2.

[21] Vandecaveye V, De Keyzer F, Vander Poorten V, Dirix P, Verbeken E, Nuyts S, et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. Radiology 2009;251:134–46. https://doi.org/10.1148/radiol.2511080128.

[22] Lambregts DM, Beets GL, Maas M, Curvo-Semedo L, Kessels AG, Thywissen T, et al. Tumour ADC measurements in rectal cancer: effect of ROI methods on ADC values and interobserver variability. Eur Radiol 2011;21:2567–74. https://doi.org/10.1007/s00330-011-2220-5.

[23] Japanese Gastric Cancer A. Japanese classification of gastric carcinoma. Gastric Cancer: 3rd English edition 2011;14:101–12. https://doi.org/10.1007/s10120-011-0041-5.

[24] Viganò L Cimino M TG, Imai K, Vibert E, Donadon M, Castaing D, Adam R. Drop-out between the two liver resections of two-stage hepatectomy. Patient selection or loss of chance? EJSO 2016;42:1385–93. https://doi.10.1016/j.ejso.2016.03.020.

[25] Vigano L, Procopio F, Cimino MM, Donadon M, Gatti A, Costa G, et al. Is tumor detachment from vascular structures equivalent to R0 resection in surgery for colorectal liver metastases? An observational cohort. Ann Surg Oncol 2016;23:1352–60. https://doi.org/10.1245/s10434-015-5009-y.

[26] Torzilli G. Ultrasound-guided liver surgery: an atlas. first ed. Milan: Springer-Verlag; 2014.

[27] Yasui O, Sato M, Kamada A. Diffusion-weighted imaging in the detection of lymph node metastasis in colorectal cancer. Tohoku J Exp Med 2009;218:177–83. http://www.ncbi.nlm.nih.gov/pubmed/19561387.

[28] Cho EY, Kim SH, Yoon JH, Lee Y, Lim YJ, Kim SJ, et al. Apparent diffusion coefficient for discriminating metastatic from non-metastatic lymph nodes in primary rectal cancer. Eur J Radiol 2013;82:e662–8. https://doi.org/10.1016/j.ejrad.2013.08.007.

[29] Heijnen LA, Lambregts DM, Mondal D, Martens MH, Riedl RG, Beets GL, et al. Diffusion-weighted MR imaging in primary rectal cancer staging demonstrates but does not characterise lymph nodes. Eur Radiol 2013;23:3354–60. https://doi.org/10.1007/s00330-013-2952-5.

[30] Lambregts DM, Maas M, Riedl RG, Bakers FC, Verwoerd JL, Kessels AG, et al. Value of ADC measurements for nodal staging after chemoradiation in locally advanced rectal cancer-a per lesion validation study. Eur Radiol 2011;21:265–73. https://doi.org/10.1007/s00330-010-1937-x.

[31] Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN. Americas hepato-pancreato-biliary association; society of surgical oncology; society for surgery of the alimentary tract. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB 2013;15:91–103. https://doi.org/10.1111/j.1477-2574.2012.00557.x.