Abdominal Radiology (2019) 44:3099–3106
https://doi.org/10.1007/s00261-019-02110-3

HEPATOBILIARY

5-Fluorouracil induced liver toxicity in patients with colorectal cancer: role of computed tomography texture analysis as a potential biomarker

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Published online: 27 June 2019

Abstract

Purpose To assess if CT texture analysis (TA) can serve as a biomarker of liver toxicity in patients with colorectal cancer treated with 5-fluorouracil (5-FU)-based chemotherapy.

Methods In this IRB-approved, HIPAA-compliant retrospective study, patients with colorectal cancer treated with 5-FU-based regimens during 2008–2010 were identified from institutional electronic database. Total 43 patients (23 women; mean age 56 years) with normal baseline liver function tests (LFTs), availability of baseline (pre-chemotherapy) and first follow-up CT (median 1.7 months, interquartile range (IQR) 1.5–2.5) performed during chemotherapy were included. Two single-slice ROI of right and left liver lobe were obtained on baseline and first follow-up CT for TA. Texture features [mean, entropy, kurtosis, skewness, mean of positive pixel, standard deviation (SD)] were extracted using a commercially available software (TexRAD; Feedback Medical Ltd, Cambridge, UK). Changes in texture parameters between baseline and follow-up CT were evaluated with Wilcoxon signed-rank test for patients with and without LFT elevation during chemotherapy.

Results Patients with LFT elevation ($n=34$; 79%) showed significantly different mean, entropy, skewness, and SD (p values range 0.007–0.047) between baseline and first follow-up CT. No significant changes in features were observed in patients without LFT elevation ($n=9$; 21%). In 19 patients (56%), first follow-up CT was performed before elevation of LFTs was observed.

Conclusions This proof-of-concept study shows that there are early changes in liver texture on first follow-up CT in patients with LFT elevation during 5-FU-based chemotherapy for colorectal cancer. In more than 50% of cases, these changes occur before LFT elevation becomes evident on blood tests.

Keywords Tomography · X-ray computed · Chemotherapy · Liver · Drug-induced liver injury

Introduction

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer death in the US, with 50,630 estimated deaths in 2018 solely in the US [1]. While for localized disease 5-year relative survival rate is 90%, for people with advanced disease the 5-year relative survival is 12% [1]. Many treatment options are available for people with advanced colorectal cancer and these often include different chemotherapy regimens in the adjuvant or neoadjuvant setting [2]. Nonetheless, the various chemotherapy regimens, including the 5-fluorouracil (5-FU)-based regimens (FOLFIRI, FOLFOX) are known to be associated with hepatic toxicity, which may range from hepatitis, steatosis, steatohepatitis, and sinusoidal obstruction syndrome

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(SOS), and are known to increase morbidity and mortality after resection [3–5]. Bevacizumab, an antibody-targeting VEGFR and with antiangiogenic effect, used as a first- or second-line treatment of metastatic colorectal cancer added to 5-FU-based regimens, is reportedly associated with a reduction in SOS and hepatic fibrosis [6–10]. Hepatotoxicities associated with chemotherapy regimens used in colorectal cancer are common, occurring in up to 47% of patients treated with 5-FU and 78% of patients treated with oxaliplatin-based chemotherapy, often presenting with only minimal elevation of liver function tests (LFTs) [5, 11–13].

Biomarkers of liver toxicity and SOS have been widely investigated. Among them, preoperative levels of aspartate aminotransferase/platelets ratio index (APRI) was proven to be predictive of severe SOS lesions and fibrosis, whereas alanine transaminase (ALT) and aspartate transaminase (AST) was associated with FOLFIRI-based hepatotoxicity [14–17]. Various imaging biomarkers of hepatotoxicity have been investigated, including splenic size and heterogeneity of liver parenchyma seen on CT for SOS. The latter was found to correlate with spleen size and APRI in patients with history of oxaliplatin-based chemotherapy [4]. Nonetheless, while all these biomarkers identified patients at risk for chemotherapy-associated hepatotoxicity, their value in predicting development of liver injury early during treatment is limited. Given that hepatotoxicity is associated with increased perioperative mortality, it would be important to identify biomarkers for the early prediction of hepatic toxicity in these patients [3].

Texture analysis (TA) is a relatively new imaging technique which quantifies tissue heterogeneity by assessing the distribution of texture coarseness and irregularity within a defined region which cannot be otherwise assessed by visual image inspection. This method has been proposed as a non-invasive marker of fibrosis, showing promising results in discriminating high and low-grade fibrotic disease, and in predicting postoperative liver insufficiency [18–21].

Given the paucity of early predictors of hepatic toxicity and the promising results of CT-based TA (CTTA) in evaluating liver injury, the purpose of this study was to assess if CT texture analysis (CTTA) can serve as a biomarker of liver toxicity in patients with colorectal cancer treated with 5-fluorouracil (5-FU)-based chemotherapy.

Materials and methods

Study population

Institutional review board approval at our institution was obtained for this retrospective HIPAA-compliant study. Informed patient consent was waived. A search of electronic medical database identified a total of 199 patients with advanced or high-risk colorectal cancer treated with 5-FU-based chemotherapy evaluated at the gastrointestinal oncology service of our institution from January 2008 to December 2010. Of these, 56 were excluded due to unavailability of baseline CT of the abdomen (performed before chemotherapy) and 35 due to unavailability of first follow-up CT (first CT performed after starting chemotherapy). Of the remaining 108 patients, 57 were excluded due to unavailability of LFTs before and after the therapy. Of a total of 51 patients, 2 patients were excluded as CT before chemotherapy was performed without intravenous contrast media administration. The 49 initially included patients were then screened for history of chronic liver disease, hepatitis, non-alcoholic fatty liver disease, alcohol abuse and presence of altered LFTs before starting chemotherapy, and six patients were excluded, due to altered LFTs before starting chemotherapy. Thus, the final study population consisted of 43 patients [20 men, 23 women; mean age 56 years (SD 14.54, range 27–84)] with normal baseline LFTs. First follow-up CT was performed at median 1.7 months [interquartile range (IQR) 1.5–2.5 months] after starting the treatment.

Clinical data and liver function tests

Age at diagnosis, sex, type of 5-FU based chemotherapy (FOLFOX, FOLFIRI), duration of chemotherapy, use of bevacizumab, presence of liver metastases before starting 5-FU based chemotherapy were recorded for every patient. Levels and dates of ALT, AST, APRI before, during and after chemotherapy (at the time of first CT after chemotherapy) were recorded and the date of initial alteration was recorded. APRI was calculated according to prior validated calculation [16] with the following formula: (AST/ULN)/PC x 100, where ULN is upper limit of the normal AST (45 IU/L) and PC is platelet count in 10^9 cells per liter. Included subjects were divided based on LFT elevation in: patients without LFT elevation during or after chemotherapy, and patients with LFT elevation (any elevation of AST, ALT or APRI, defined as > 45 IU/L, > 52 IU/L and > 0.36, respectively) during or after chemotherapy. Any elevation in LFTs, rather than three times the upper limits of normal, was considered abnormal because patients with 5-FU-related hepatic toxicity often present with only minimal elevation of LFTs [5, 11–13].

CT acquisition

Due to the retrospective nature of the study, CT image parameters and protocols varied among selected patients; however, all the CTs met the following minimum criteria: contrast-enhanced CT scans of the abdomen obtained with spiral technique; multidetector scanners (4–128 detectors); 120–140 kVp; 40–80 mAS; 3–5 mm slice thickness using

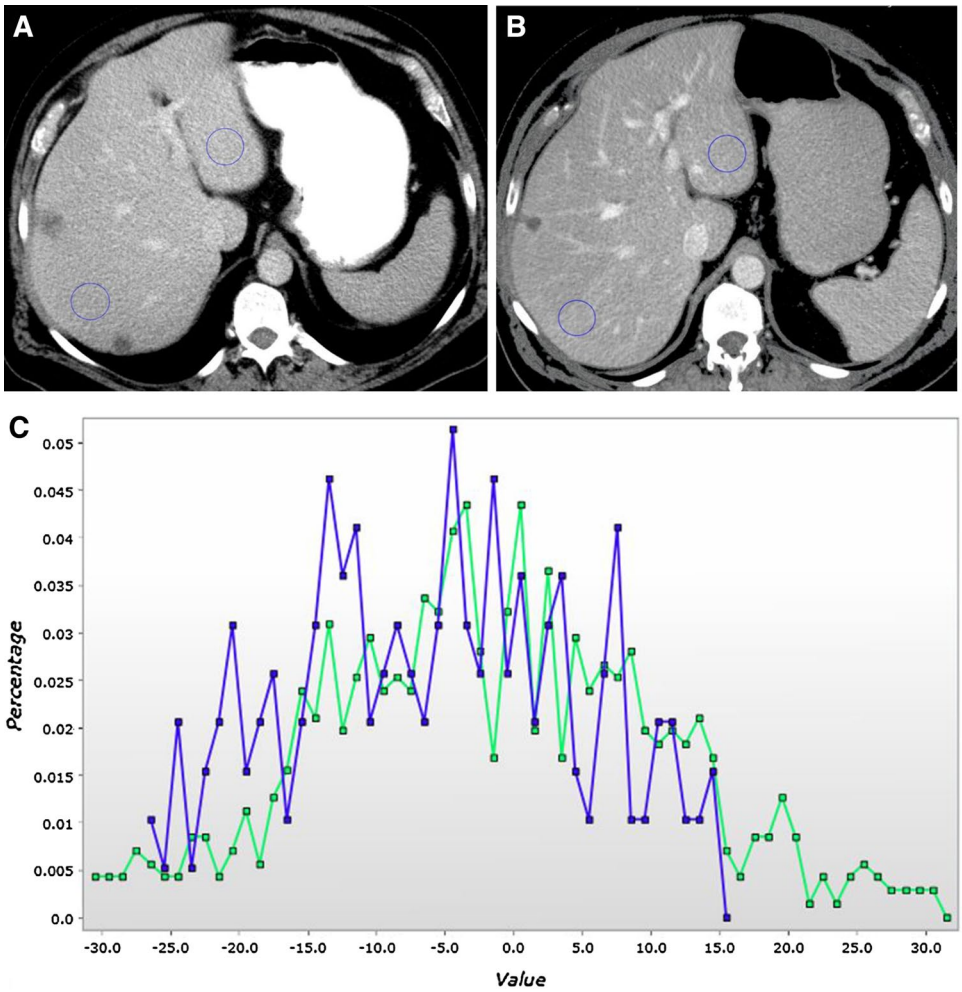

Fig. 1 56-year-old man in-patient without elevation of liver function tests during FOLFOX chemotherapy. **a** Baseline axial CT image acquired during portal venous phase showing region of interest (ROI) on the right and left liver lobes. **b** First follow-up axial CT image acquired during portal venous phase showing ROI on the right and left liver lobes. **c** Comparison of the two relative filtration histograms at spatial scaling factor 5. The distribution of the pixel values on baseline CT (green) and first follow-up CT (blue) are similar, with no significant changes in the texture parameters evaluated for this filter

soft tissue reconstruction algorithm and imaging in portal venous phase, acquired 60–90 s after intravenous contrast media administration. Prior studies have shown that variation of the technical parameters in image acquisition has limited effect on the texture analysis method used in this study [22]. Baseline CT and first follow-up CT were evaluated.

CT Texture analysis

Texture analysis was performed by a single fellowship-trained radiologist with 5 years of experience (blinded for review) under the supervision of another fellowship-trained abdominal radiologist with 10 years of experience (blinded for review). The radiologists were aware of history of colorectal cancer being treated with 5FU-based therapy, but were blinded to other clinical parameters including any changes in LFTs. A single CT image acquired during portal venous phase at the level of the porta hepatis was sent to a commercially available texture analysis research software platform (TexRAD Ltd, part of Feedback Plc, Cambridge, UK, www.texrad.org). Using this software, two 2 cm round ROIs were drawn on the right and left lobe of the liver, excluding major vessels and any liver lesions. Care was taken to make sure the size and locations of the ROIs were the same for baseline and first follow-up CTs (Figs. 1, 2). The CTTA technique employed in this study uses a previously reported filtration histogram technique [18].

This technique evaluates the gray-level frequency distribution from the pixel intensity in a given area of interest, retrieving a set of quantifiable texture features. The pixel intensity is plotted on a histogram with frequency of occurrence of a determined value of pixel intensity [23–25]. After ROIs were drawn, the following statistical-based histogram parameters were calculated:

1. Mean: the average value of the pixel intensities within the ROI;
2. Standard deviation (SD): measures how much variation or dispersion exists from the mean value;
3. Entropy: a measure of irregularity or complexity of pixel intensities;

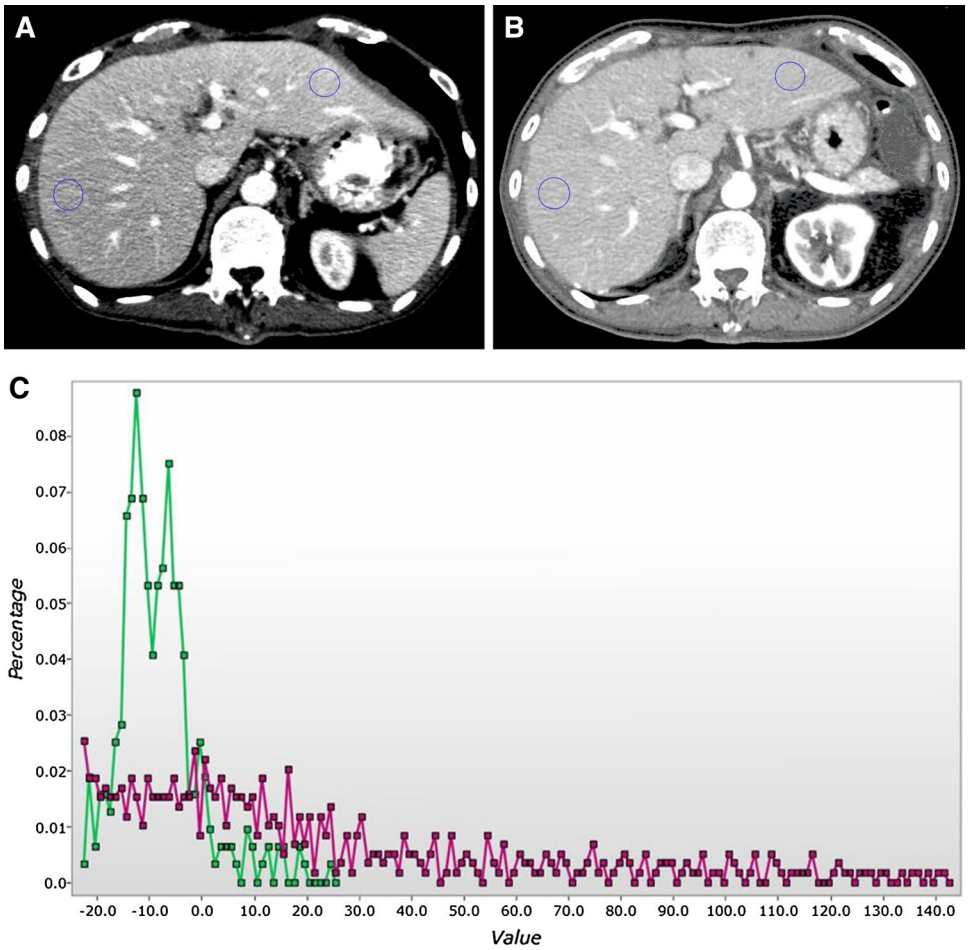

Fig. 2 72-year-old man in patient with elevation of liver function tests during FOLFOX chemotherapy. **a** Baseline axial CT image acquired during portal venous phase showing region of interest (ROI) on the right and left liver lobes. **b** First follow-up axial CT image acquired during portal venous phase showing ROI on the right and left liver lobes. **c** Comparison of the two relative filtration histograms at spatial scaling factor 5. The distribution of the pixel values on baseline CT (pink) differs from the distribution of first follow-up CT (green). The different shapes of the histogram reflect elevation in entropy (irregularity or complexity of pixel intensities) and standard deviation (variation or dispersion from the mean value) of the pixel distribution for this filter

4. Mean of the positive pixels (MPP): average gray-level of the pixel intensity values on the histogram above threshold of zero;
5. Skewness: a measure of the asymmetry of the distribution of the pixel intensity values on the histogram;
6. Kurtosis: a measure of the peakedness of the of the distribution of the pixel intensity values on the histogram [23, 24].

These features were quantified at different spatial scaling factors (SSF) ranging from fine (SSF2), medium (SSF3,4,5) to coarse (SSF6). These histogram parameters were also quantified from the conventional CT image without filtration (SSF0). The histogram parameters of the right and left liver lobe of each patient were calculated separately, and the mean values were reported for each patient.

Statistical analysis

Descriptive statistics were produced for the demographic and clinical characteristics of cases. Mann–Whitney test was used to compare each texture parameter on baseline CT and on first follow-up CT scan between patients with and without LFT elevation during chemotherapy. Same comparisons were also made between patients with different chemotherapy regimens (FOLFOX vs. FOLFIRI), presence of liver metastases and with or without added bevacizumab on first follow-up CT.

Texture parameters measured on baseline CT and on first follow-up CT were compared for patients with and without LFT elevation during chemotherapy separately, using Wilcoxon signed-rank test for paired data. All p values were based on a two-sided hypothesis. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using JMP® Software (JMP®, Version 13.0.0 SAS Institute Inc., Cary, NC, 1989–2007).

Results

Patient characteristics

Baseline characteristics of the patients are presented in Table 1. Total 20 patients had evidence of liver metastases before starting 5-FU-based chemotherapy. Median duration of initial 5-FU-based chemotherapy was 5.5 months

Table 1 Clinical and laboratory characteristics of included patients

Characteristic	Patients (n = 43)
Gender	
Men	20
Women	23
Age (years—mean, SD)	56 ± 14.54
Presence of hepatic metastasis before starting chemotherapy	20
Chemotherapy duration (median, interquartile range- months)	5.5 (4–7)
Chemotherapy regimen	
FOLFOX	34
FOLFIRI	9
Added bevacizumab	32
Elevation of liver function tests	
No elevation	9 (21%)
Any elevation	34 (79%)

SD standard deviation

occurred, a median of 17 days before in these patients (IQR 42.5–83 days, range 2–161 days).

In patients with elevated LFTs, median AST was 40.5 IU/L (IQR 21.75–48.0 IU/L), median ALT was 46 IU/L (IQR 20.5–61.75 IU/L), median APRI was 0.42 (IQR 0.31–0.725) during chemotherapy, and 21.5 IU/L (IQR: 18-30.5 IU/L), 18 IU/L (IQR 13–32 IU/L), and 0.28 (IQR 0.17–0.42) at the end of chemotherapy, respectively. In patients without LFT elevation, median AST was 17 IU/L (IQR 12.25–21 IU/L), median ALT was 13 IU/L (IQR 11.5–13 IU/L), median APRI was 0.19 (IQR 0.16–0.2).

Texture analysis

Texture parameters and association with elevated liver function tests

No significant difference was observed on baseline CT (p values range 0.11–1) and on first follow-up CT between patients with and without elevation of LFTs during chemo-

Table 2 Changes in texture parameters in patients with liver function test elevation during chemotherapy between baseline CT and first follow-up CT

Patient group SSF	Baseline CT [median; IQR]	First follow-up CT [median; IQR]	p value
Texture parameter			
SSF0			
SD	12.47 [11.19 to 14.05]	11.51 [10.56 to 13.72]	0.04
Entropy	3.82 [3.73 to 3.91]	3.73 [3.62 to 3.89]	0.04
SSF2			
Mean	−0.03 [−0.96 to 0.57]	0.18 [−0.41 to 0.93]	0.047
Entropy	4.48 [4.38 to 4.62]	4.41 [4.31 to 4.53]	0.03
SSF3			
Mean	−0.05 [−1.2 to 1.07]	0.45 [−0.36 to 1.78]	0.007
SSF4			
Mean	0.45 [−0.88 to 2.35]	1.09 [−0.13 to 3.62]	0.04
SSF5			
Skewness	0.34 [0.02 to 0.74]	0.09 [−0.1 to 0.42]	0.02
SSF6			
Skewness	0.23 [0.07 to 0.85]	0.17 [−0.43 to 0.51]	0.03

SSF spatial scaling factor, *SD* standard deviation, *IQR* interquartile range

(IQR 4–7 months). Median interval between baseline-first follow-up CT was 2.5 months (IQR 2.0–3.4 months). When subdivided based on LFT elevation during and after chemotherapy, 9 (21%) patients had no LFT elevation during and at end of chemotherapy, and 34 (79%) patients had elevation of LFTs during or at the end of chemotherapy. First follow-up CT was performed a median of 17 days before elevation of LFTs was observed (IQR: 65 days before elevation of LFTs-27.5 days after elevation of LFTs). In 19/34 patients (56%), first follow-up CT was performed before LFT elevation

therapy (p values range 0.07–0.94).

When changes in texture parameters from baseline to first follow-up CT were evaluated, SD entropy, mean, and skewness were significantly different in patients with LFT elevation (Table 2). In brief, SD was significantly different without filter (SSF0) (p value 0.04); entropy was significantly different without filter (SSF0) (p value 0.04) and for fine filter (SSF2) (p value 0.03), mean for fine and medium filters (SSF2,3,4) (p values 0.047, 0.007, 0.04, respectively);

Table 3 Comparison between texture parameters at first follow-up CT in patients with or without added bevacizumab and with or without liver metastases before starting chemotherapy

Patient group SSF	Yes [median; IQR]	No [median; IQR]	*p*-value
Texture parameter			
Bevacizumab			
SSF2 Mean	0.15 [−0.48 to 0.95]	−0.98 [−1.13 to 0.13]	0.01
SSF3 Mean	0.45 [−0.6 to 1.78]	−0.82 [−1.67 to −0.18]	0.0009
Liver metastases			
SSF2 Entropy	4.46 [4.4 to 4.53]	4.37 [4.25 to 4.51]	0.02
SSF3 Entropy	4.15 [4.09 to 4.23]	4 [3.91 to 4.19]	0.01
SSF4 Entropy	4 [3.88 to 4.11]	3.84 [3.67 to 3.97]	0.03
SSF6 Kurtosis	0.65 [−0.85 to −0.06]	−0.21 [−0.64 to 0.75]	0.04

SSF spatial scaling factor, *IQR* interquartile range

and skewness for medium (SSF5) (p value 0.02) and coarse filters (SSF6) (p value 0.03).

No significant difference in texture parameters were observed in patients without LFT elevation from baseline CT to first follow-up CT were observed (p values range 0.1–0.98).

Association with chemotherapy regimens and liver metastases

No significant difference was observed between TA parameters of patients treated with different chemotherapy regimen (FOLFOX vs. FOLFIRI) (p values range: 0.09–0.99).

In patients treated with bevacizumab, mean for fine and medium filters (SSF2,3) were significantly different from patients treated without added bevacizumab (p values 0.01, 0.009) (Table 3).

In patients with liver metastases, entropy for fine and medium filters (SSF2,3,4) (p values = 0.02, 0.01, 0.03 respectively), and kurtosis for coarse filter (SSF6) (p value = 0.04) on first follow-up CT were significantly different from patients without liver metastases before starting chemotherapy (Table 3).

Discussion

Liver toxicity is a known event associated with 5FU-based therapy routinely used for colorectal cancer. Besides elevated LFTs, there are no known reliable biomarkers of drug-induced liver toxicity. Even the predictive value of LFTs early in development of hepatotoxicity is limited, since these are elevated after injury has already occurred [26]. This proof-of concept study showed that patients treated with 5-FU-based chemotherapy with LFT elevation demonstrated increased heterogeneity of the liver on CT texture analysis during treatment, with changes in SD, entropy, mean and skewness from baseline to first follow-up CT and that texture changes preceded LFT elevation in more than 50% of cases. While the exact mechanism remains unknown, the changes in texture parameters likely reflect the increase in underlying heterogeneity of the liver parenchyma secondary to chemotherapy-associated liver toxicity.

Various studies have investigated the biomarkers of liver toxicities in patients treated with 5-FU-based combination regimens [14, 15, 27]. A study on 156 patients treated with FOLFIRI showed significant increase in AST and ALT levels early during treatment, 3 months after treatment was started [17]. Subsequently, a study on 151 patients who underwent liver resection for metastatic colorectal cancer investigated the factors predictive of severe SOS, showing that APRI and splenomegaly were predictive of more severe SOS and showed that bevacizumab had a protective effect on the severity of SOS [14]. Park et al. recently correlated 5-FU chemotherapy-associated changes of noninvasive liver fibrosis indices, including APRI, with spleen size, demonstrating good correlation between the two [28]. A recent study from Han et al. on patients treated with oxaliplatin-based chemotherapy found that the severity of the heterogeneity of liver parenchyma, measured qualitatively on CT images acquired during portal venous phase, correlated with a number of chemotherapy cycles and was associated with increase in AST, ALT, APRI values and spleen size [5]. Interestingly, a more recent study from the same group, showed that heterogeneity of the liver parenchyma is a predictor of tumor response [29]. In view of the previous studies, which showed good correlation between noninvasive markers of 5-FU toxicity and evidence of fibrosis and SOS on liver resections, we used AST, ALT and APRI as a surrogate gold standard to define chemotherapy-associated liver toxicity, in view that hepatotoxicity often present with only minimal elevation of these biomarkers [26].

The role of TA has been widely studied for the evaluation of response to treatment in various cancers [16, 30–32]. Regarding the use of TA for evaluation of diffuse liver disease, a recent study by Daginawala et al. explored the role of TA in differentiating various degrees of hepatic fibrosis, showing that high-grade fibrosis had higher SD, entropy, mean and median values when compared with low-grade fibrosis [20]. Lubner et al. investigated the role of TA to detect the presence of hepatic fibrosis and its correlation with fibrosis stage. In this study on 289 adults, mean

correlated with fibrosis for all TA filters used, SD for fine filters, entropy for fine, medium and coarse filters, and kurtosis and skewness only for coarse filters [19]. In our study, increase in APRI, a marker of liver fibrosis, was associated with increased SD without filter, entropy without filter and for fine filters, mean for fine and medium filters, and skewness for coarse filters when evaluated on CT performed early during chemotherapy. Interestingly, we did not see any difference in kurtosis which was significantly higher in patients with fibrosis in the previous studies. This might be related to the different methods in which ROIs were obtained: we had drawn two separate round ROIs on the right and left lobe of the liver, excluding major vessels and liver lesions, while other studies had drawn multiple ROIs contouring the whole liver in different slices.

Bevacizumab is reported to have a protective effect on development of liver toxicity in patients treated with oxaliplatin; we found that mean for fine and medium filter was significantly lower in patients treated with bevacizumab added regimens compared to patients without bevacizumab, suggesting the possible protective role bevacizumab for liver toxicity, as increased mean has been previously associated with higher grade of fibrosis [6–9, 14, 15, 20].

In patients with liver metastases, entropy for fine and medium filters, and kurtosis for coarse filter on first follow-up CT significantly differed from patients without liver metastases before starting chemotherapy. These findings might reflect the changes in TA parameters occurring in liver parenchyma of patients with liver metastases [32].

Regarding possible predictive role of TA for liver toxicity, Simpson et al. investigated the role of TA in predicting hepatic insufficiency in patients undergoing liver resection, showing that correlation (linear dependency of gray levels on neighboring pixels) and entropy were higher in patients with postoperative hepatic insufficiency [23]. In our study, patients with elevation of LFTs during chemotherapy showed that entropy was increased for different filters (SSF0,2), on CT performed early during chemotherapy.

In addition, in our cohort, in 19 patients (56%), elevation of LFTs was observed after first follow-up CT was performed, suggesting that changes in liver texture may occur before elevation of LFT become evident, although larger studies are needed to confirm this preliminary finding.

This study has several limitations, including its retrospective nature. No pathologic data were available, thus elevation of LFTs was used as a surrogate to define 5-FU-associated liver toxicity, which is the standard clinical practice as liver biopsy is not practical in every patient. In addition, various studies have shown good correlation between liver fibrosis or SOS and elevation of AST, ALT or APRI [14–16]. To avoid confounders, patients with underlying liver disease were excluded. We performed CTTA on only two ROIs on a single CT slice, and evaluation might have been influenced by the presence of uneven fat infiltration. Nevertheless, caution was taken to maintain the same size and locations of the ROIs for baseline and first follow-up CTs, so to limit variability for each patient. Finally, our study population was small, as only few patients had CT performed early during chemotherapy which may have limited the ability of this study to identify additional significant difference in texture parameters, and yet we found a significant difference in liver texture despite the small numbers. Of these, only 56% had CT performed before LFT elevation, thus the predictive role of CT for drug-associated hepatic toxicity is limited in our study.

Conclusion

This exploratory study indicates that there are early texture changes in the liver parenchyma in patients who are experiencing hepatic injury during 5-FU-based therapy, seen as early as at first CT after starting the chemotherapy and may serve as an imaging biomarker of hepatic toxicity, and in more than half of patients these become evident before other signs of hepatic injury.

Larger prospective studies exploring correlations with invasive and noninvasive markers of 5-FU-associated hepatotoxicity are needed to further investigate these preliminary findings, to define the role of CTTA as a biomarker of liver toxicity.

Compliance with ethical standards

Conflict of interest Francesco Alessandrino, Sonia Sahu, Gisele Cruz, Lei Qin, Michael H. Rosenthal and Jeffrey A. Meyerhardt, no related financial relationships to disclose. Atul B. Shinagare Consultant, Arog Pharmaceuticals; research funding, GTx Inc.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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