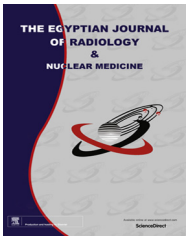
The Egyptian Journal of Radiology and Nuclear Medicine (2016) **47**, 693–698

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

www.elsevier.com/locate/ejrnm
www.sciencedirect.com



ORIGINAL ARTICLE

Multi-detector computed tomography (MDCT) findings of chemotherapy induced hepatic changes

Sieza Samir Abd-Allah [a,*], Ahmad El-Morsy [a], Adel El-Badrawy [a], Magdy Settein [a], Shahira El-Etreby [b], Amal Halim [c], Tawfik Elkhodary [d], Sameh M. Abdel Monem [e]

[a] *Radiology Department, Mansoura Faculty of Medicine, Mansoura, Egypt*
[b] *Internal Medicine Department, Mansoura Faculty of Medicine, Mansoura, Egypt*
[c] *Clinical Oncology & Nuclear Medicine Department, Mansoura Faculty of Medicine, Mansoura, Egypt*
[d] *Medical Oncology Department, Mansoura Faculty of Medicine, Mansoura, Egypt*
[e] *Tropical Medicine Department, Zagazig Faculty of Medicine, Zagazig, Egypt*

Received 20 February 2016; accepted 7 May 2016
Available online 4 June 2016

KEYWORDS

MDCT;
CT;
Chemotherapy liver

Abstract *Purpose:* To evaluate the role of multi-detector computed tomography (MDCT) in detection and characterization of chemotherapy induced hepatic changes.
Materials and methods: This retrospective study included 400 patients with confirmed 14 malignancies and treated by standard chemotherapy regimens. The most common malignancy was non-Hodgkin lymphoma and mostly chemotherapy regimen was Cyclophosphamide, Hydroxydaunomycin, Oncovin and Prednisolone (CHOP). All patients underwent CT scan using 64 MDCT scanner (Brilliance 64, Philips) before chemotherapy and follow-up after 6 months from last session of chemotherapy. Precontrast series and post-contrast triphasic study were done for all patients. All the patients underwent radiological evaluation for hepatic changes after chemotherapy treatment. All CT scans were evaluated for fatty liver, capsular retraction, venoocclusive disease and biliary sclerosis. Four patients with capsular retraction underwent liver biopsy.
Results: Forty patients (32 females and 8 males) had hepatic changes due to effect of chemotherapy. The most common CT finding was fatty liver. Hepatic fatty changes were detected in 36/40 patients. These fatty changes were diffuse, focal fatty and diffuse with fatty spare area. Four patients had capsular retraction: 1 patient with HD and 3 patients with metastatic cancer breast. Veno-occlusive disease and biliary sclerosis were not detected.

Abbreviation: MDCT; Multidetector computed tomography.

* Corresponding author.
E-mail addresses: Sieza_s@mans.edu.eg (S.S. Abd-Allah), Dr.a.elmorsy@gmail.com (A. El-Morsy), adelelbadrawy@hotmail.com (A. El-Badrawy), magdysettein@hotmail.com (M. Settein), Aly_shahira@yahoo.com (S. El-Etreby), amalsalahm@yahoo.com (A. Halim), Tawragab2005@yahoo.com (T. Elkhodary), drsameh154@yahoo.com (S.M. Abdel Monem).

Peer review under responsibility of The Egyptian Society of Radiology and Nuclear Medicine.

http://dx.doi.org/10.1016/j.ejrnm.2016.05.007

1. Introduction

Chemotherapy as the main nonsurgical remedy of cancer treatment is generally based on the cytotoxic effect of natural or synthetic agents taking advantage of a higher vulnerability of cancer cells as compared to normal cells. However, normal cells may be affected by cytotoxic chemotherapy as well (1).

Cancer chemotherapy has evolved from cytotoxic agents and now includes several new agents that target specific molecules responsible for the regulation of cell growth, nutrient supply, and differentiation. These molecularly targeted therapies have a different mechanism of action than do classic cytotoxic agents, which predominantly attack rapidly proliferating cells. Therefore, the toxicities of targeted and cytotoxic agents may differ in both clinical and radiological presentations (2).

The final effect of all these drugs is to inhibit cell division in rapidly dividing cells and thereby reduce the cell turnover in cancer tissues. Unfortunately, these drugs can also affect the normal cells, especially those with rapid cell division, leading to significant complications. That is why the GIT and bone marrow are more susceptible to injury in patients undergoing cytotoxic chemotherapy. However, it may affect any organ in the body (3).

Chemotherapy related hepatic complications are relatively common. The spectrum of pathology ranges from reversible hepatic steatosis to advanced cirrhosis and vascular injury (4).

The purpose of this study was to evaluate the role of MDCT in detection and evaluation of chemotherapy induced hepatic changes, differentiation of these changes from progression of the disease and/or super added pathology.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board, and informed consent was waived. This retrospective study included 400 patients (206 females and 194 males). The complaint of the 400 patients at time of presentation was variable and ranged from loss of weight to palpable masses. Some of these cases were complaining of more than one symptom. The clinical presentations of the 400 patients are represented in Table 1. These patients presented with 14 different malignancies and were treated by standard systemic chemotherapy regimens without loco-regional chemotherapy between January 2014 and December 2015 (Tables 2 and 3).

Those patients were referred to perform abdominal CT scans before and after chemotherapy regimens as follow-up studies. All patients underwent three or more follow-up CT scans from 1st session of chemotherapy. Laboratory evaluation for liver function test, tumor markers, serum amylase and serum creatinine was done.

2.2. MDCT imaging

All patients underwent precontrast and triphasic CT scan using 64 multi-detector CT scanner (Brilliance 64; Philips Healthcare, Best, Netherlands). The precontrast series was taken by using a 5 mm slice thickness. Triphasic post-contrast study was done using 120 ml of low osmolar

Table 1 Clinical presentation of 400 patients.

Clinical presentation	No. of cases	Percentage
Headache, nausea and vomiting	16	4
Neck swelling	36	9
Breast mass	32	8
Progressive loss of weight	264	66
Epigastric pain	32	8
Hematuria	2	0.5
Vaginal bleeding	2	0.5
Difficulty in swallowing	2	0.5
Constipation and abdominal distention	14	3.5
Total	400	100

Table 2 The distribution of primary tumors according to patient sex.

Primary lesion	Distribution according to sex of the patient		Total
	Male	Female	
NHL	134	100	234 (58.5%)
HD	26	22	48 (12%)
Breast	–	32	32 (8%)
Colon	8	6	14 (3.5%)
Ovary	–	20	20 (5%)
Stomach	6	8	14 (3.5%)
Bladder	2	–	2 (0.5%)
Pancreas	12	6	18 (4.5%)
Esophagus	–	2	2 (0.5%)
Germ cell	2	2	4 (1%)
CLL	2	2	4 (1%)
Osteosarcoma	2	–	2 (0.5%)
Neuroblastoma	–	4	4 (1%)
Endometrial carcinoma	–	2	2 (0.5%)
Total	194	206	400 (100%)

Table 3 Different chemotherapy regimens used in 400 patients.

Chemotherapy regimen	Number of cases
CHOP	196 Patients (49%)
DHAP	18 Patients (4.5%)
ABVD	34 Patients (8.5%)
FAC	32 Patients (8%)
ABVD + MINE	10 Patients (2.5%)
DHAP + MINE	6 Patients (1.5%)
ABVD + CHOP	6 Patients (1.5%)
DHAP + ICE	8 Patients (2%)
BEA-COPP	8 Patients (2%)
FOLFOX	12 Patients (3%)
ECF	8 Patients (2%)
CISPLATINE + TAXANE	20 Patients (5%)
CISPLATINE + GEMZAR	26 Patients (6.5%)
CISPLATINE + 5-FLUROURACILE	8 Patients (2%)
CISPLATINE + ENDOXANE	8 Patients (2%)
Total	400 (100%)

Table 4 Clinical presentation at time of diagnosis chemotherapy complication.

Clinical presentation	No. of cases	Percentage from affected cases	Percentage from total cases
Asymptomatic	24	60	6
Easy fatigability and loss of appetite	8	20	2
Abdominal pain	4	10	1
Abdominal enlargement	4	10	1
Jaundice	0	0	0
Total	40	100	10

non-ionic contrast medium (ioversol, Optiray 350) at a flow rate of 5 ml/s; then, the CT scan was performed with the following acquisition parameters 200 mAs, 120 kVp, 512 × 512 matrix, 1.172 pitch, 64 × 0.625 mm section collimation, 2 mm slice thickness, 1 mm reconstruction increment. All images were transferred to the workstation [Extended Brilliance Workspace V3.5.0.2254] (EBW) for post processing.

2.3. Image analysis

Abdominal CT images were evaluated retrospectively using Picture Archiving and Communication System (PACS, Paxeramed, Paxeramed Corp, Oslip, Austria) for all patients before and after chemotherapy regimens to differentiate between progression of malignancy and chemotherapy changes.

The imaging analysis was based on source images. Data interpretation was based on consensus of at least two radiologists with 15 years duration experience of abdominal imaging. The precontrast images were used to measure the liver attenuation index (LAI) by inserting multiple ROI in the liver and spleen avoiding major vessels. Fatty infiltration of the liver is diagnosed if the difference between average liver attenuation

Table 5 The clinical data and the radiological findings for 40 cases.

Primary tumor	Hepatic radiological findings	Chemotherapy	Chem./Dose	Pat. No.
Breast Car.	Diffuse fatty	FAC	6 Cycles	7
Breast Car.	Capsular retraction/pseudo-cirrhosis	FAC	8 Cycles	3
NHL	Focal fatty infiltration	CHOP	5 Cycles	3
NHL	Diffuse fatty	CHOP	8 Cycles	5
NHL	Diffuse fatty	CHOP	4 Cycles	8
HD	Diffuse fatty	ABVD	6 Cycles	2
HD	Capsular retraction/pseudocirrhosis	CHOP	6 Cycles	1
Ovarian Car.	Diffuse fatty	Endoxan & platinol	4 Cycles	4
Pancreatic Car.	Diffuse fatty	GEMZAR	7 Cycles	2
Colonic Car.	Fatty liver with fatty sparing area	FOLFOX	3 Cycles	2
Acute ML	Diffuse fatty	CHOP	4 Cycles	2
Endometrial Car.	Diffuse fatty	Cisplatin/Taxol	6 Cycles	1
				40

Pat. No.: Patients' Number.
NHL: Non-Hodgkin Lymphoma.
HD: Hodgkin Disease.
ML: Myeloid leukemia.
Car.: Carcinoma.

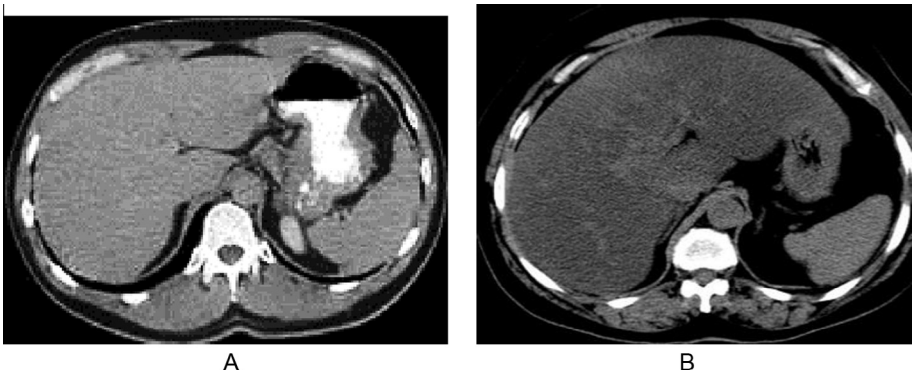


Fig. 1 44-Years-old female patient underwent mastectomy for cancer breast and received 6 cycles of FAC. Abdominal CT scan was done. (A) Post oral and before IV contrast abdominal CT scan before starting chemotherapy regimen which is normal. (B) Non-contract abdominal CT scan, 6 months after starting chemotherapy regimen which revealed diffuse hepatic fatty infiltration (hypodense liver parenchyma).

and the average spleen attenuation is less than or equal to 10 HU on non-enhanced scans. Liver attenuation index (LAI) is defined as the difference between mean hepatic and mean splenic attenuation (5,6).

Post-contrast abdominal CT scans were used to detect response to treatment (regression or progression) differentiating this from chemotherapy induced hepatic changes such as fatty liver, capsular retraction, veno-occlusive disease and biliary sclerosis. Four patients with capsular retraction underwent liver biopsy.

In patients with capsular retraction, measurements of the depth of the retraction, if present, were obtained by measuring the greatest distance from the hepatic capsule to its expected course and perpendicular to a line through the hepatic capsule.

Follow-up abdominal CT scans after chemotherapy of the 400 patients were reviewed and compared with other CT abdominal scans obtained before starting chemotherapy regimes.

3. Results

From the 400 patients 290 patients showed no changes induced by chemotherapy detected in their abdominal CT scans. The other 110 patients were carefully re-evaluated, comparing findings detected in their abdominal CT scans with the clinical data, laboratory investigations and pre-chemotherapy CT scans to know whether these changes were related to the chemotherapy or progression of the disease and/or superadded pathology. Final results (by exclusion of other possibilities as newly developed hepatic focal lesions even if with fatty changes) confirmed that only 40 patients (with a percentage of 10% of total cases) reported to have changes in liver which are indeed due to effect of chemotherapy. The most common chemotherapy regimen used was CHOP and the most common finding was fatty liver. The 40 patients were 32 females and 8 males. Their ages ranged from 40 years up to 70 years old. Clinical observation of the 40 patients resulted in 24 patients of them were asymptomatic and accidentally discovered during routine follow-up by abdominal CT scans (Table 4). Eight patients presented with easy fatigability and loss of appetite. Eight patients present with abdominal pain and abdominal enlargement.

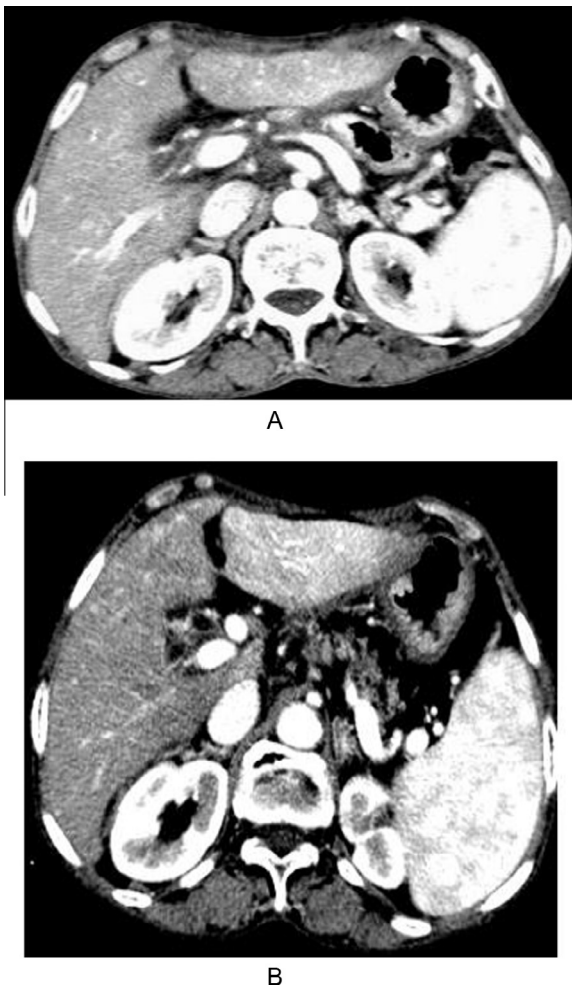


Fig. 3 70-Years-old female with colonic carcinoma received 3 cycles of FOLFOX. Triphasic CT scan was done. (A) (Late arterial phase) before starting chemotherapy regimen which revealed normal liver and spleen. (B) (Late arterial phase) 6 months after starting chemotherapy regimen which revealed enlarged and diffuse hypodense liver parenchyma (lower than the spleen) sparing small area of left liver lobe (fat sparing area); enlarged spleen was also noticed.

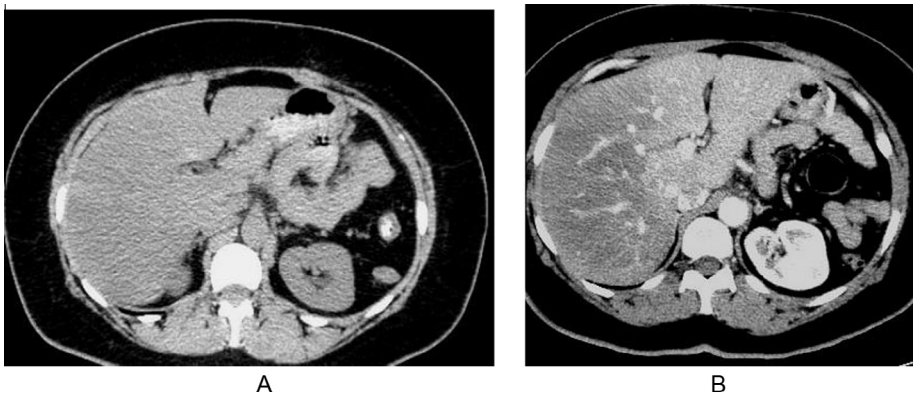


Fig. 2 43-Years-old female patient with NHL and received 6 cycles of CHOP. Abdominal CT scan was done. (A) Non-contrast abdominal CT scan axial cut (A) before starting chemotherapy regimen which is normal. (B) Arterial phase abdominal CT scan 6 months after starting chemotherapy regimen revealed focal fatty infiltration of right liver lobe (hypodense right liver lobe parenchyma).

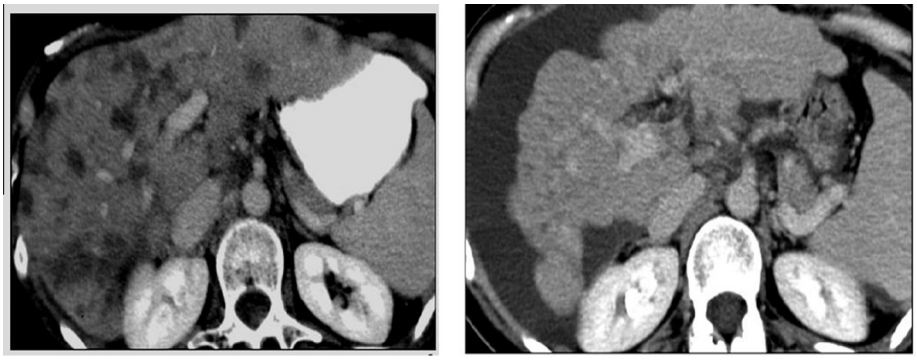


Fig. 4 45-Years-old female patient underwent mastectomy for cancer breast and received 8 cycles of FAC. Abdominal CT scan was done. (A) Portal phase before starting chemotherapy regimen revealed: multiple small hypodense lesions scattered all over the liver (metastatic). (B) Delayed phase, 6 months after starting chemotherapy revealed: marked decrease size and number of metastatic lesions with significant capsular retraction which mimic cirrhosis (pseudo cirrhosis) and ascites.

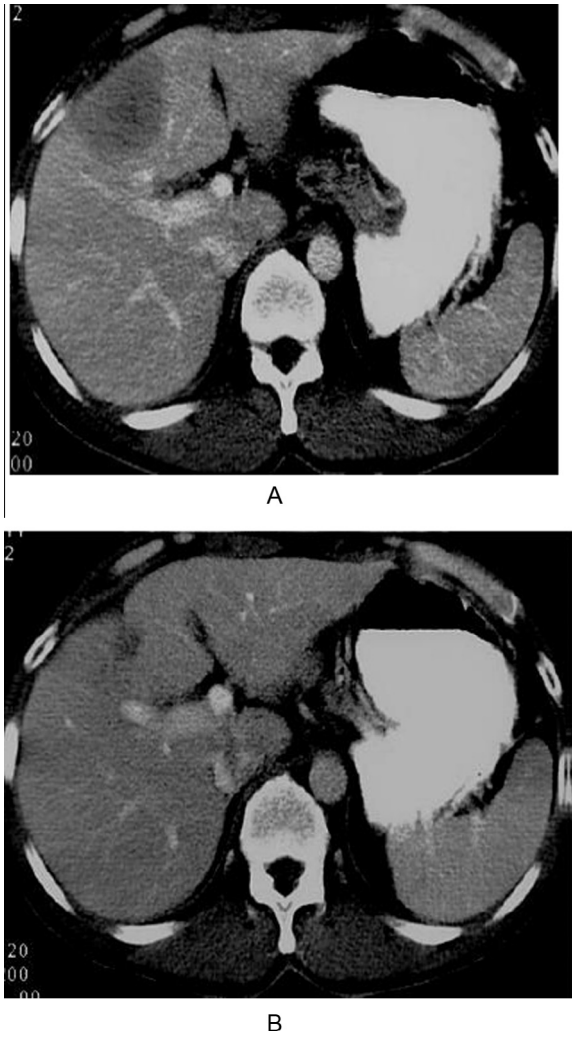


Fig. 5 57-Years-old female with HD received 6 cycles of CHOP. Triphasic abdominal CT scan was done. (A) (Portal phase) before starting chemotherapy shows a non-enhancing focal lesion of segment IV, biopsy revealed HD. (B) (Portal phase) obtained 6 months after starting of chemotherapy shows capsular retraction of the liver. The size of the hepatic mass is markedly decreased.

The CT changes were hepatic fatty changes in 36/40 patients (Table 5). Fatty changes were diffuse (31 patients), focal fatty (3 patients) and diffuse with fatty spare (2 patients) (Figs. 1–3). Four patients had capsular retraction (Figs. 4 and 5). Capsular retraction ranged in depth from 2 mm in 1 patient with HD to 10–13 mm in 3 patients with metastatic cancer breast. Veno-occlusive disease and biliary sclerosis were not detected.

4. Discussion

Cancer therapy has significantly improved in the past few decades with development of various newer classes of cytotoxic chemotherapy as well as novel, molecularly targeted chemotherapy. However, both these treatments affect the tumor as well as the normal tissues, lead to significant toxicity. These side effects range from mild to life threatening, and may involve multiple organs. Imaging plays an important role in the early identification of such complications, which may allow more effective patient management (3).

Advancements in imaging have led to recognition of radiological features of previously unsuspected diseases. Occasionally, imaging may also identify effects of treatments instituted for these diseases. Consequently, MDCT plays a critical role in the accurate diagnosis of a broad spectrum of drug-induced complications in the abdomen, in both emergent and nonemergent settings. Knowledge of the natural history, clinical manifestations, and salient imaging features of these entities is crucial to facilitate accurate clinical diagnosis in a timely fashion (7).

As the center of metabolism, the liver is susceptible to a wide array of drug-related injuries. Hepatic steatosis is the most common among them. It may be seen in nearly 20% of patients undergoing treatment with certain forms of chemotherapy (8). Steatosis may progress to steatohepatitis, characterized by additional evidence of inflammation and fibrosis.

On CT, fatty infiltration typically has a well-defined, geometric pattern. On unenhanced CT scan, the attenuation of the liver will be lower than the spleen due to the deposition of fat within the hepatocytes, and the Hounsfield unit measurement may be less than 40. Further, the intrahepatic vasculature

appears hyperattenuating against the liver parenchyma on unenhanced CT scan in the presence of severe steatosis (9).

In our study we compared pre- and post-chemotherapy abdominal CT studies and detect changes appeared on liver which were not seen in pre-chemotherapy CT studies differentiating them from disease progression. Liver parenchyma appeared low attenuated than spleen in precontrast CT study. In our study we detected diffuse fatty liver in 31 cases, focal fatty infiltration in 3 cases and diffuse fatty liver with fatty spare areas in 2 cases.

Our findings are in agreement with Shanbhogue et al. (7). In our study, we detected fatty infiltration of the liver in 36/400 (9%) patients. Fatty infiltration was seen in different patterns focal, diffuse and fat sparing. Biopsy was taken from equivocal cases to confirm diagnosis. The difference was between our study and that of Peppercon et al. (8) due to selection of certain forms of chemotherapy. But, in our study there is no selection of chemotherapy.

Advanced stages of hepatocellular injury may rarely progress to cirrhosis or pseudo cirrhosis. Pseudocirrhosis, characterized by marked distortion of architecture with dense fibrosis is typically seen with metastatic breast cancer or lymphoma after prolonged chemotherapy, and chemotherapy for pancreatic cancer (10,11).

This was reported in our study in 3 cases with metastatic breast cancer treated by 8 cycles of FAC and developed significant capsular retraction (pseudo cirrhosis). One case of HD with hepatic focal lesion was treated by 6 cycles of CHOP and developed mild capsular retraction adjacent to the lesion which decreased in size.

Blachar et al. (12) stated that, cirrhosis manifests as shrunken nodular liver with atrophic right and medial left lobes and hypertrophy of caudate and lateral left lobes. Pseudo cirrhosis appears similar to cirrhosis on imaging, and this was clear in 3 cases of our study.

Wide spread capsular retraction was found in 3/32 (9.4%) cases of metastatic cancer breast underwent FAC. This is in agreement with previous study (13) who found this finding in 10/91 (11%). Fennessy et al. found hepatic capsular retraction in 50% of patients with hepatic metastases of cancer breast (14). This difference from our study 3/32 is due to small number of our cases and different chemotherapeutic regimens.

The pathological results of 3 cases with significant capsular retraction revealed nodular regenerative hyperplasia which is characterized by forming regenerative hepatic nodules with compression and atrophy of intervening parenchyma but without hepatic fibrosis. This was in agreement with previous studies (3,15).

In our study, veno-occlusive disease and biliary sclerosis were not detected as a complication of chemotherapy, and these not coincide with previous results reported by Robinson (10) who reported that these complications were seen after direct infusion of chemotherapeutic agents inside hepatic artery; this method was not used with patients included in our study.

4.1. Conclusion

MDCT can accurately detect and evaluate chemotherapy induced hepatic changes, differentiation of these changes from progression of the disease and/or super added pathology. Fatty liver is the commonest hepatic induced changes. Awareness of chemotherapy induced hepatic changes can help the radiologist to detect these at early stages, which helps in appropriate management.

Conflict of interest

The authors declare that they have no conflict of interest.

References

(1) Ramadori G. Effects of systemic chemotherapy on the liver, department gastroenterology and endocrinology, 2010.
(2) Jean MT, Lawrence SS, Marc JG, et al. CT findings of chemotherapy- induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology, 258, 2011. p. 41–56.
(3) Dhakshina MG, Chitra V, Aparna B, et al. Complications of oncologic therapy in the abdomen and pelvis. Abdom Imag 2012;38(1):1–21.
(4) Torrisi JM, Schwartz LH, Gollub MJ, et al. CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology 2011;258:41–56.
(5) Limanond P, Raman SS, Lassman C, et al. Macrovesicular hepatic steatosis in living related liver donors: correlation between CT and histologic findings. Radiology 2004;230(1):276–80.
(6) Park SH, Kim PN, Kim KW, et al. Macrovesicular hepatic steatosis in living liver donors: use of CT for quantification and qualitative assessment. Radiology 2006;239:105–12.
(7) Shanbhogue AK, Virmani V, Vikram R, et al. Spectrum of medication-induced complications in the abdomen: role of crosssectional imaging. AJR Am J Roentgenol 2011;197(2): W286–94.
(8) Peppercorn PD, Reznek RH, Wilson P, Slevin ML, Gupta RK. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer 1998;77:2008–11.
(9) Hamer OW, Aguirre DA, Casola G, et al. Fatty liver: imaging patterns and pitfalls. Radiographics 2006;26(6):1637–53.
(10) Robinson PJ. The effects of cancer chemotherapy on liver imaging. Eur Radiol 2009;19(7):1752–62.
(11) Viswanathan C, Bhosale P, Ganeshan DM, Truong MT, Silverman P, Balachandran A. Imaging of complications of oncological therapy in the gastrointestinal system. Cancer Imag 2012;12:163–72.
(12) Blachar A, Federle MP, Sosna J. Liver lesions with hepatic capsular retraction. Semin Ultrasound CT MR 2009;30 (5):426–35.
(13) Qayyum A, Lee GK, Yeh BM, Allen JN, Venook AP, Coakley FV. Frequency of hepatic contour abnormalities and signs of portal hypertension at ct in patients receiving chemotherapy for breast cancer metastatic to the liver. Clin Imag 2007;31(1):6–10.
(14) Fennessy FM, Mortele KJ, Kluckert T, et al. Hepatic capsular retraction in metastatic carcinoma of the breast occurring with increase or decrease in size of subjacent metastasis. AJR 2004;182:651–5.
(15) Shirkhoda A, Baird S. Morphologic changes of the liver Following chemotherapy for metastatic breast carcinoma: CT findings. Abdom Imag 1994;19(1):39–42.