

Effect of Chemotherapy on Liver Metabolism as Measured by PET/CT scan

Shaimaa A. Ahmed¹; AIDA Salama²; Mohamed Mohamed Houseni ³; Asmaa A A Elsheshiny⁴

¹*Biophysics Branch, Physics Department, Faculty of Science (Girls branch), Al-Azhar University, Cairo,* ²*Biophysics Branch, Physics Department, Faculty of Science (Girls branch), Al-Azhar University, Cairo,* ³*Radiology Department, National Liver Institute, Menoufia University, and* ⁴*Biophysics Branch, Physics Department, Faculty of Science (Girls branch), Al-Azhar University, Cairo, Egypt*

The aim of this study was to investigate the metabolic changes on liver caused by chemotherapy by utilizing F¹⁸-FDG PET/CT scan. Seventy-eight patients with lymphoma underwent 18F-FDG PET/CT scan before, after treatment and in follow up stage. Hounsfield unit (HU) of liver and spleen, maximum and mean standard uptake value (SUV_{max}, SUV_{mean}), mean correlation for background, metabolic tumor volume (MTV), total lesion glycolysis (TLG) were elevated. A radiomics's analytical system (LIFEx v.4) was used in the study to generate four histogram-intensity features. Image texture analysis was done using six gray levels co-occurrence matrix (GLCM).

Forty-five patients (57.7%) during treatment had liver morphologic changes (changes in the structure of the organ) according to HU of liver and spleen from non contrast CT, HU of liver in CT scan with contrast and liver volume. There are functional changes in SUV_{max}, MTV, and TLG. There are also morphological changes proved by first order statistics [histogram features (skewness, entropy, and kurtosis)]. Increasing number of cycles of chemotherapy lead to textural changes proved by second order statistics [GLCM features (homogeneity, energy, contrast, correlation, entropy and dissimilarity)].

Most of features from F¹⁸-FDG PET/CT provide strong independent predictors for fatty liver changes in patients with lymphoma under chemotherapy. The utility of such features should be confirmed by larger clinical studies before considering their potential integration into decisional algorithms aimed at personalized medicine.

Introduction

Chemotherapy has long been used for treating cancer patients. Chemotherapy works by killing the fast growing cells in the body. Investigators have also shown that dying tumor cells induce anticancer immune response (1). Chemotherapy has significant organ toxicities. There are two side effects of chemotherapy: 1) damage to the normal cells results from drug toxicities and 2) debilitating side effects like pain, nausea, fatigue, vomiting, hair loss, mouth and throat sores, anemia, depression and increased risk of infection (2). Among cytotoxic agents, alkylating agents were the first to be used as chemotherapy in

lymphomas. Corticosteroids are sometimes used together with chemotherapy because they have both a lympholytic and antiemetic effect. Cytotoxic agents may be used as single agents but most commonly they are used in various combinations. Topoisomerase inhibitors and antimetabolites are also used as chemotherapy drugs (3).

Positron emission tomography (PET) is one of the most important techniques for human body imaging which was widely used. As PET scan is a sensitive agent for detecting tumor, it can be also effective in imaging healthy tissue. Combining Computed tomography (CT) with

*Corresponding author : shaimaaabdullah142@gmail.com

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PET scan has the advantage of adding metabolic information to the anatomic information. By adding contrast to PET/CT, it can provide fully diagnostic morphologic and functional data in a single session (4). The main usage of PET/CT scan is to assess the tumor's treatment response to chemotherapy(5). We believe that more research is needed to study the effect of chemotherapy on body organs so, the aim of the present work was to evaluate the effect of different types of chemotherapy given to patients with lymphoma and to study how it affects liver metabolism utilizing PET/CT scan images with analysis done using radiomics analysis system.

Radiomics, is a method of extraction of high number of features from medical images. This includes texture analysis and shape analysis which involves the highthroughput extraction of quantitative imaging features to create mineable database from radiological images(6). In general, all this features are designed to build descriptive and predictive models of every patient during treatment tour. This application is usually used for analysis of tumor cells but here we will use it in the analysis of healthy organs in patient images. The main thesis of radiomics is that these models which included biological and functional data can provide useful diagnostic, prognostic or predictive information (7).

Materials and Methods

Patients

The present study include 78 patients who are diagnosed with lymphoma, range of age is 20-80 years, while the gender is 38 men and 40 women. All Patients undergo PET/CT scan 3 times at the initial stage, after chemotherapy and follow up stage. The interval between the first scan and the second one was about 5 months (after 6 cycles). At follow up stage, some of patients do the scan after 6 months while the rest do it after 12 months (8).

¹⁸F-FDG PET/CT acquisition

All PET/CT scans are done using Siemens Biograph PET/CT unit (20 detectors). Patient clinical historical data are recorded for each patient including body weight and blood sugar. Patients are requested to fast six hours before the scan and they were only allowed to drink water. Blood test is done to insure that the maximum blood glucose level is not exceeding 200mg/dl. Scan start after about 60 minutes (rang 40-55 min.) after intravenous injection of ¹⁸F-FDG.

The injected dose is dependent on body weight (Body weight \times 0.14) per Kg. Image acquisition is done as follows: 1) First, low dose CT scan is done starting from the base of the skull to the mid-thigh (no intravenous contrast, 3mm slice thickness; 100 Kv tube voltage, 30 to 80 mAs tube current depending on body weight, and pitch= 1.0), 2) Second, a PET emission image taken for about 20 min (scan is set to 2 min. per couch position), 3) Finally, CT scan is taken with contrast (60 to 100 ml/kg) contrast agent, (0.75mm slice thickness; 100 Kv tube voltage, 150 to 220 mAs tube current and pitch=1.0). All images reconstructed according to European Association of Nuclear Medicine Research Limited (EARL) guidelines for both PET and CT image sets.

Patients' workflow:

¹⁸F-FDG PET/CT analysis:

After image reconstruction, the liver which is the region of interest (ROI) is manually drawn and then we started our analysis measurements, image analysis is done for all patients in two ways: 1- From the low dose CT image set, we measured the HU of liver and HU of spleen. From the CT with contrast image set, we measured the HU and the volume of liver. From PET emission image set, we measured the SUVmax, SUVmean, mean correlation for background, MTV and TLG, inside the segmented ROI, and we also calculated the total lesion glycolysis (TLG).

2- From the PET image set and the use of the radiomics system application, we generated three histogram features (skewness, entropy, and kurtosis) and textural GLCM features (homogeneity, energy, contrast, correlation, entropy, and dissimilarity)(9).

Semi-automated segmentation of liver

It should be mentioned that analysis was done by experienced radiologist and nuclear physician. Only in case of liver, segmentation is done using a semi-automated method. ROI was drawn to include the majority of the organ of interest with caution not to exceed organ boundary in order to reduce random noise. Tumor or an organ tracer uptake is assessed using standard uptake value (SUV) which is a semi-quantitative parameter defined as the ratio of radio-activity concentration to the injected dose normalized for body weight (10). Two measurements were done at two different locations of the ROI to reduce the potential errors from selecting certain region. The first ROI was placed at the dome in the right lobe in the largest

area of the liver, and the second was placed at the blood pool at the distal descending thoracic aorta. SUVmax and the mean was determined. These measurements of SUV values were then analyzed using a paired one-way analysis of variance test to determine their variation with respect to dynamic SUV values (11). Hounsfield units are a relative quantitative measurement of radio density used by radiologists in the interpretation of computed tomography (CT) image (12). Fig. (1) On the left, is a CT scan image without contrast showing HU of liver and spleen. On the right, CT scan image with contrast shown volumetric image for liver and HU of liver. MTV was defined as total tumor volume with an SUV of 2.5 or greater, and the MTV and mean SUV of the ROI were automatically calculated. TLG was calculated as (mean SUV) where $TLG = SUV_{mean} \times MTV$ (13).

Features extraction by radiomics (LIFEx)

After the ROI was selected, the radiomics application converted the image into 3D geometry and started image analyzing. Histograms are then generated (relation between activity (SUV) and number of voxels). Among these parameters, four first order features (liver volume, skewness, entropy, and kurtosis) and six second order

GLCM features (homogeneity, energy, contrast, correlation, entropy, and dissimilarity) all based on different matrices capturing the spatial intensity distributions at different scales (14).

First order statistics represent the distribution of the individual voxels of the image without concern for spatial relationships. These are the histogram based method which reduce the ROI to single values for SUV, liver volume, skewness (asymmetry), entropy (randomness), and kurtosis (flatness) of the histogram values. Second order statistics represent the texture features (GLCM), the inter relationships between voxels with similar or dissimilar contrast values. These textural GLCM features are homogeneity (closeness of the distribution of element in matrix), energy (the uniformity of gray level voxels pairs), contrast (local intensity variation away from the normal), correlation (measure of GL linear dependence between pixels at specific position in relative to each other), entropy (measure the degree of randomness within the pixel intensities), and dissimilarity (variation of grey level voxel pairs) (15). As shown in Fig. (2) is example of radiomic's analysis showing a histogram of the activity (SUV) values.

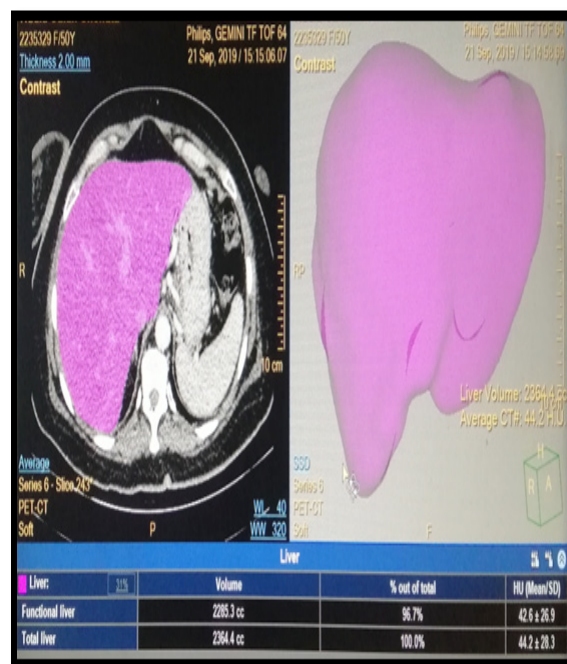
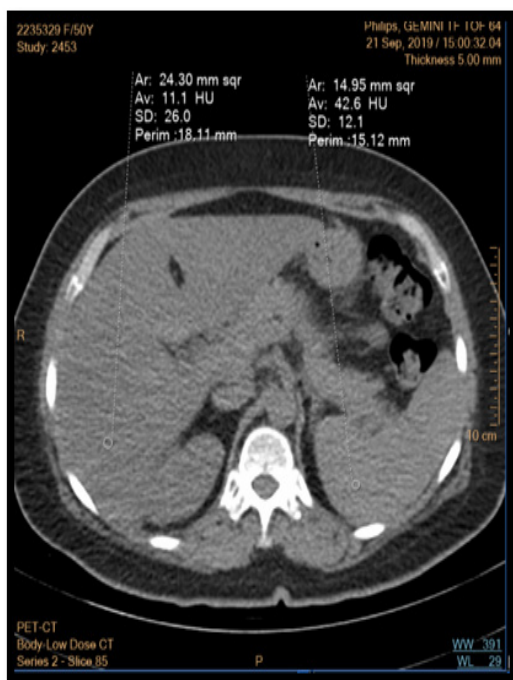


Fig. 1. CT image of liver showing HU of liver & spleen from low dose scan, liver volumetry and HU of liver from CT with contrast.

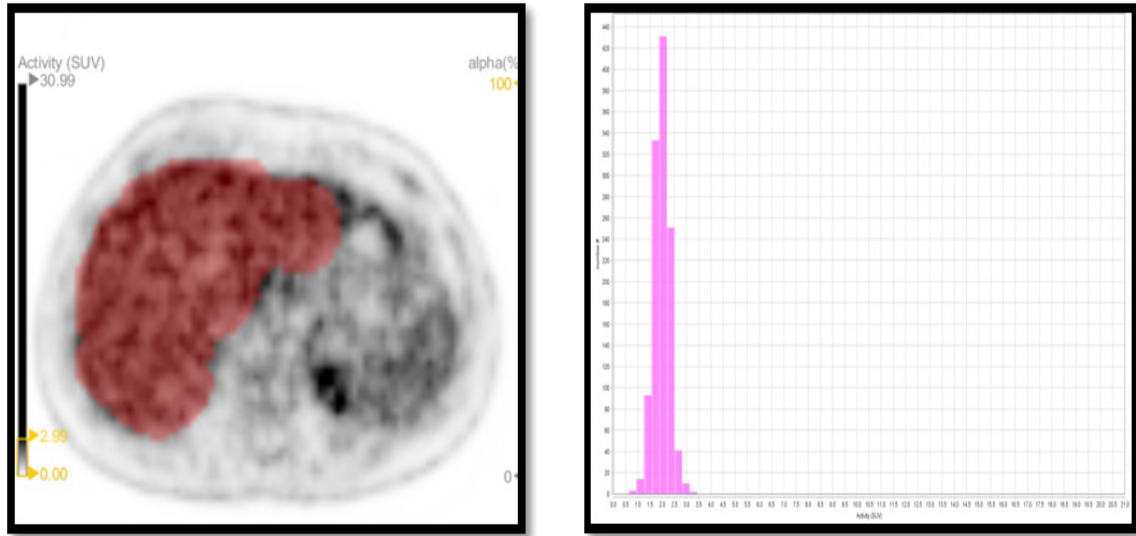


Fig. 2. Radiomics analysis showing a histogram of activity (SUV) values for a patient liver .

Statistical analysis

Data were reported as continuous variables and were described as the means \pm SUV, with median values. Summary statistics were reported on each patient individually by using T.test and P.test statistical. Statistical significance between HU of liver and spleen was reported by SPS statistical package. Results were considered statistically significant at the 95% critical level ($P < 0.05$). All statistical analyses were performed using the SPS statistical package (16).

Results

Table 1 summarizes patient data as well as treatment and scan parameters. The 78 patients included 38 males and 40 females, age ranged from 20 to 80 years. The time interval between first and second scan was about 150 days. Patients have taken 6 cycles of chemotherapy. Patients were divided into two main groups 1) 45 patients who responded to treatment with fatty changes in liver, 2) control group contains 33 patients responded to treatment with minimum changes in measurement and no liver changes.

	78
Male/female	38/40
Age	range(20-80)
Diagnosis	Lymphoma
Treatment	Chemotherapy
Number of cycles	6
Scan time	Mean 25 min
Number of scanning for each patient	3
Scan period	5 months
Follow up period	6-12 months
Normal HU of liver	Mean (40-60)
Normal HU of spleen	Less than 40

The initial scans that were done before treatment showed that HU of liver is greater than that of spleen; however, after chemotherapy, HU of liver became less than that of spleen in 45 patients. It was also notice that as chemo cycles increases that difference increase. Some patients started treatments with fatty liver and for those we studied weather the liver condition will change with chemotherapy or not. No effect was seen in the liver in 33 patients.

Figure 3 shown an example of patients' low dose CT scans done in the 3 stages; initial, after chemo cycles, and at follow up. The difference in

HU and MTV of liver and HU of spleen can be seen in the three stages.

Figure 4 shows an example of patient CT scans showing no significant difference in HU values between all stages for the liver and spleen.

Figure 5 shows a patient with a liver that recovered to normal state (HU of liver > HU of spleen) 6 months after treatment. Liver HU value was less than that of spleen during treatment. Then it became larger in follow up stage indicating that the fatty changes on liver was due to chemotherapy (17).

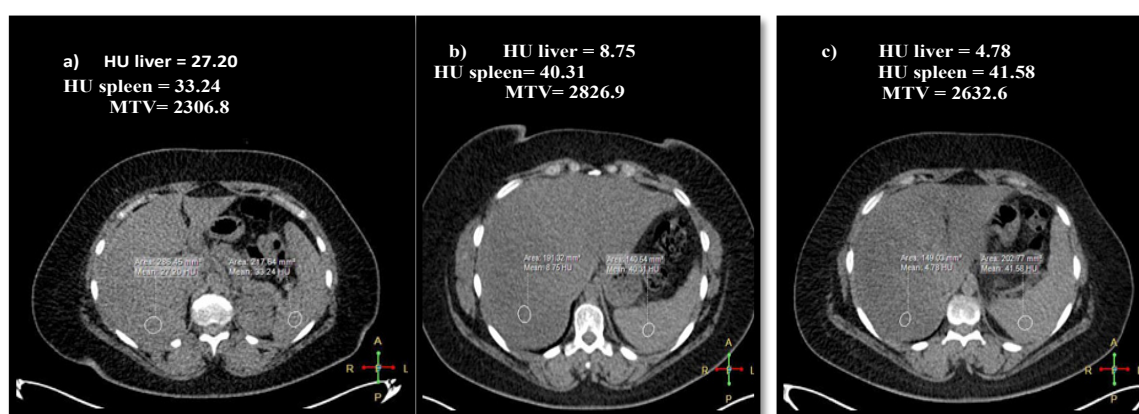


Fig. 3. CT scans done in 3 stages; initial, after chemo cycles, and at follow up showing changing in HU and MTV of liver and HU of spleen, a) initial scan, b) scan after chemo cycles, c) scan at follow up.

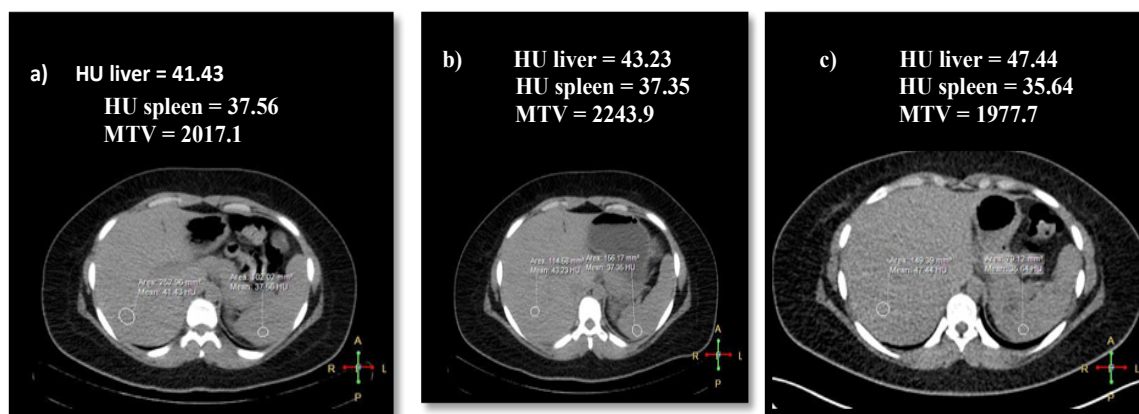


Fig. 4. CT scans done in 3 stages; initial, after chemo cycles, and at follow up showing no difference in HU and MTV of liver and HU of spleen, a) initial scan, b) scan after chemo cycles, c) scan at follow up.

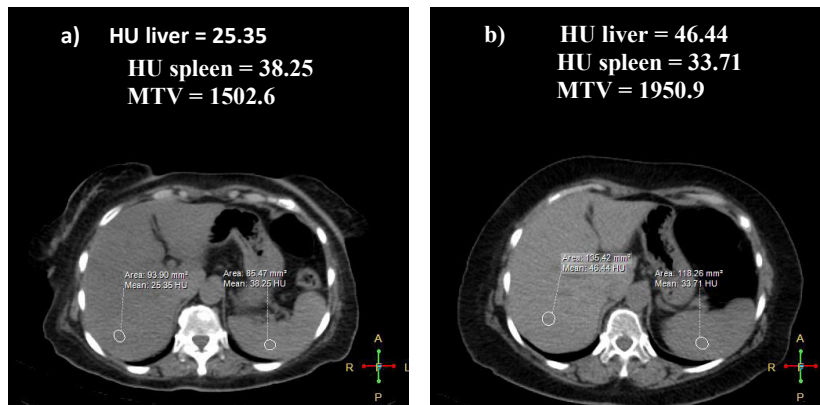


Fig. 5. CT scans done in 2 stages; after chemo cycles, and at follow up showing Patient had liver recovery to normal state in HU and MTV of liver and HU of spleen, a) scan after chemo cycles, b) scan at follow up.

It is found from the statistical analysis of results that there are significant *morphological changes* of liver as shown in Table (1), for all patients that have taken chemotherapy (45 cases) when compared with the control group (33 cases). A significant decrease in HU of values was seen in the liver with the contrast and non-contrast CT images. A significant change was also observed in liver volume. There were no changes in HU of spleen. Table 2 is a comparison with respect to *metabolic parameters* and significant changes is seen between the two groups on all parameters. *Radiomics* analysis summarized in Table 3, showed less significant difference between the two groups. Features like skewness, GLCM homogeneity, GLCM energy, GLCM contrast, and GLCM dissimilarity were showing normal values before and after chemotherapy.

Table (4) summarizes the observed changes in the volume and fat content of liver for all patients. The degree of change was divided into mild, moderate and severe, and this was done in comparison with the patients in control group. In patients who finished chemotherapy, 35 showed fatty changes in the liver while 10 did not show changes. The degree of fatty liver changes in the 35 patients was as follows: 13 cases mild fatty changes, 10 moderate fatty changes and 12 cases had severe fatty changes. In control group only 3 patients showed fatty changes. On the other hand, liver volume increased in 36 patients while remained unchanged in 9 patients. The degree of volume change in the 36 patients was as follows; 11 mild increases in liver volume, 12 cases moderate and 13 cases severe increase in liver volume. In the control group, only 3 cases had increase in liver volume (18).

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Discussion

In regards to our research work, it should be mentioned that other investigations have conducted research to study the liver changes with drugs. For example, *Robinson et al.*, studied the late effect of chemo on patients as observed in their CT scans. They found that the response of liver to any foreign drug is different from one patient to another. In most cases the liver damage disappears once the drug is withdrawn. They have seen that steatosis (fatty changes) was the most common side effect of drug hepatotoxicity and represents the form of liver damage which can be recognized by imaging. On CT without contrast, fatty liver was showing paranchymal attenuation changes which are proportionately to the steatosis. By CT with contrast the enhancement of liver attenuation was more variable but the fatty changes in liver can be detectable (19).

Rao, et al., studied the relative changes in texture parameters 50 patients who underwent CT scan before and after chemotherapy treatment. They observed changes in entropy (which measure heterogeneity in the gray level distribution) and uniformity (which measure homogeneity of gray level distribution) in Radiomics. However, in our study we have seen changes after treatment in the kurtosis, entropy, GLCM entropy and GLCM correlation. All of these parameters are considered as predictors to differentiate any changes in liver before and after treatment (20).

TABLE 1. Morphological changes.

	Cases under chemotherapy Number of cases: 45					Control group Number of cases: 33					P value
	Mean	SD	Median	95% CI From	To	Mean	SD	Median	95% CI From	To	
HU of liver (non contrast)	Base line	41.52	8.17	41.00	40.70	42.35	4.56	43.80	43.16	44.15	0.16
	After 6 cycle	23.15	12.76	24.70	21.86	24.43	6.55	50.35	48.60	50.04	<0.0001*
HU of spleen (non contrast)	Base line	39.39	7.09	39.60	38.68	40.11	4.90	39.85	38.49	39.57	0.79
	After 6 cycle	41.06	6.88	41.50	40.37	41.76	4.01	39.00	38.61	39.49	0.12
HU of liver (contrast)	Base line	62.12	13.05	64.15	60.79	63.45	13.64	76.40	73.26	76.24	0.17
	After 6 cycle	49.34	13.01	47.20	48.03	50.64	10.82	78.20	74.31	76.67	<0.0001*
Volume (cc)	Base line	2087.55	507.50	2061.70	2035.94	2139.15	538.11	1965.80	1922.18	2039.94	0.36
	After 6 cycle	2384.05	563.95	2375.60	2326.70	2441.39	513.18	1902.45	1853.95	1966.25	<0.0001*

TABLE 2. Metabolic Parameters.

	Cases under chemotherapy Number of cases: 45					Control group Number of cases: 33					P value
	Mean	SD	Median	95% CI From	To	Mean	SD	Median	95% CI From	To	
SUVmax	Base line	3.90	0.94	3.80	3.81	3.99	8.62	2.95	3.56	5.45	0.64
	After 6 cycle	3.65	0.72	3.50	3.58	3.72	0.80	3.20	3.20	3.38	0.03*
TLG	Base line	5439.38	1809.89	5272.40	5257.40	5621.36	1187.47	5352.85	4998.80	5258.66	0.37
	After 6 cycle	5889.53	1842.98	5835.60	5704.22	6074.83	1281.86	3839.25	3698.99	3979.51	<0.0001*
MTV	Base line	2523.34	668.50	2322.60	2456.13	2590.56	562.53	2276.20	2294.96	2418.06	0.22
	After 6 cycle	2777.74	709.63	2826.90	2706.38	2849.09	587.21	2013.20	1998.95	2127.46	<0.0001*

TABLE 3. Radiomics.

P value	Control group Number of cases: 33				Cases under chemotherapy Number of cases: 45							
	95% CI		Median	SD	Mean	95% CI		Median		SD	Mean	
	To	From				To	From					
0.50	0.23	0.01	-0.01	0.97	0.12	0.32	0.17	0.08	0.76	0.25	Base line	Skewness
0.46	-0.10	-0.22	-0.25	0.54	-0.16	-0.05	-0.12	-0.03	0.38	-0.08	After 6 cycle	After 6 cycle
0.59	4.23	3.93	3.55	1.39	4.08	4.06	3.72	3.55	1.69	3.89	Base line	Kurtosis
0.01*	4.68	4.21	3.92	2.14	4.44	3.71	3.59	3.60	0.60	3.65	After 6 cycle	After 6 cycle
0.35	2.05	1.94	1.99	0.46	1.99	2.41	2.34	2.40	0.34	2.38	Base line	Entropy
<0.0001*	2.09	2.02	2.04	0.34	2.06	2.42	2.36	2.34	0.30	2.39	After 6 cycle	After 6 cycle
0.34	0.73	0.71	0.72	0.06	0.72	0.66	0.65	0.65	0.06	0.66	Base line	GLCM
0.21	0.71	0.69	0.70	0.06	0.70	0.69	0.68	0.67	0.07	0.68	After 6 cycle	Homogeneity
0.10	0.13	0.12	0.11	0.05	0.12	0.11	0.10	0.08	0.06	0.10	Base line	GLCM
0.23	0.12	0.11	0.11	0.06	0.12	0.15	0.13	0.10	0.09	0.14	After 6 cycle	Energy
0.57	4.74	1.63	0.87	14.21	3.19	2.32	1.57	1.34	3.73	1.94	Base line	GLCM
0.20	1.11	1.00	0.97	0.51	1.05	1.24	1.14	1.21	0.49	1.19	After 6 cycle	Contrast
0.22	0.55	0.53	0.52	0.11	0.54	0.58	0.56	0.57	0.12	0.57	Base line	GLCM
0.01*	0.53	0.51	0.52	0.07	0.52	0.57	0.55	0.54	0.07	0.56	After 6 cycle	Correlation
0.43	3.68	3.51	3.62	0.77	3.60	4.40	4.28	4.38	0.61	4.34	Base line	GLCM
0.05*	3.83	3.69	3.77	0.64	3.76	4.10	3.97	4.15	0.64	4.04	After 6 cycle	Entropy
0.08	0.77	0.65	0.62	0.58	0.71	0.93	0.86	0.86	0.34	0.89	Base line	GLCM
0.12	0.73	0.68	0.69	0.19	0.70	0.80	0.75	0.80	0.21	0.78	After 6 cycle	Dissimilarity

TABLE 4. Liver changes.

	Control group Number of cases: 33		Cases under chemotherapy Number of cases: 45	
		<u>Fatty changes</u>		
	3		35	Yes
			13	Mild
			10	Moderate
			12	Severe
<0.0001*	30		10	No
		<u>Increased volume</u>		
	3		36	Yes
			11	Mild
			12	Moderate
			13	Severe
<0.0001*	30		9	No

Drugs are cytotoxic agent making their effect by infiltrating cell division. Because of tumor cell are more active and its mitosis are faster than that of normal cell, it is more sensitive to drugs than normal cell. The side effect of different drugs can be observed in different tissues and body organs. These toxic reactions include gastrointestinal toxicity, nephrotoxicity, neurotoxicity, cardio-toxicity, hematological toxicity and hepatotoxicity. In our work we were only concerned with hepatotoxicity. Several drugs can cause liver damage such as cisplatin and oxaliplatin which can damage the abilities of the liver sinusoidal and destroy the blood vessels that transport oxygen to liver. The reason of hepatotoxicity is that they produce reactive oxygen species (ROS) from mitochondria in sinusoidal epithelial cells. These ROS increase cytokines and make normal hepatocytes more sensitive to apoptosis and cell damage(21).

Steatohepatitis is a fatty liver disease characterized by liver inflammation and accumulation of fats. Nowadays, significant efforts have been made to decrease the load of such disease by knowing what causing it. Tarantino, et al., stated that by looking the different types of liver treatment, i.e., causal treatment, prophylactic treatment and symptomatic treatment, they cannot stress that the most appropriate is only the first one(22). Brunner, et al., found that weight loss can improve Steatohepatitis and vitamin E, as anti inflammatory medication can improve histological features of Steatohepatitis if it mixed with chemotherapy(23).

Conclusions

The treatment of lymphoma can be done with several types of chemotherapeutic combination. These drugs have beneficial effect of killing tumor cells, but it also has the side effect on healthy organs. Measuring HU of liver and spleen, TLG, MTV and the textural analysis of F¹⁸-FDG PET/CT image, can provides strong independent predictors to follow the changes in liver after chemotherapeutic agent enter the body. In most of cases, after 6 cycles of treatment, there are fatty changes in liver and this changes increase if the number of cycles increases. Some of patients after the end of treatment, their liver recovered again as was seen in follow up which means that the changes in liver was caused by the chemotherapy. That fatty change can lead after time to the apoptosis and necrosis of hepatocytes, which can then lead to fibrosis. By careful consideration of patients' drug dose, or the time period between each cycle and the others, or adding antibodies with drugs to help reduce the side effect. All of these options may help to reduce the side effect of chemotherapy under supervision patients' doctor. These features should be validated in larger clinical studies before considering their integration in decisional algorithms, in order to contribute to achieving personalized medicine to help the patient's doctor to see the effect of chemotherapy on the tumor as well as healthy organs.

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تأثير العلاج الكيميائي على التمثيل الغذائي للكبد بواسطة المسح الذري البوزيتروني و الأشعة المقطعية

شيماء عبدالله أحمد * ، عابدة سلامة * ، محمد محمد حسيني ** و اسماء عبدالغفار الشيشيني*
قسم الفيزياء- كلية العلوم- جامعة الأزهر (فرع البنات) و **معهد الكبد القومي- جامعة المنوفية*

العلاج الكيميائي من أهم أنواع العلاج الذي يستخدم في علاج مرضى السرطان. هو كباقي الأدوية لها إيجابيات وسلبيات تختلف أعراضها من شخص لآخر تبعاً لحاله المريض الصحية والنفسية. العلاج الكيميائي يعطى للمريض عن طريق الفم أو بالحقن تحت الجلد. هناك أعراض جانبية يمكن ملاحظتها خلال فترة العلاج كتساقط الشعر وفقدان الشهية والوزن و أرق ليلي وحساسية مفرطة بالجسم. ولكن ماذا يحدث للأعضاء السليمة بداخل جسم الإنسان عند تعرضها للعلاج الكيميائي؟ تم اختيار الكبد كعضو حيوي في جسم الإنسان وظيفته تنقية الدم من السموم والمعادن الزائدة عن حاجة الجسم لدراسة تأثير العلاج الكيميائي عليه بمرضى سرطان الغدد الليمفاوية. هناك فحص مهم جداً يتم عمله قبل وأثناء وبعد العلاج لمعرفة مدى استجابة الجسم للعلاج ألا وهو المسح الذري البوزيتروني و الأشعة المقطعية باستخدام المادة المشعة فلورين 18 المحمل على فلورودى- أوكسى-جلوكوز. فهي تقنية للتصوير تستخدم لقياس الطاقة المنبعثة من المادة المشعة التي يتم حقنها للمريض قبل إجراء الفحص. و هو أيضاً تقنية تستخدم لتصوير تغيرات الأيض ووظائف الجسم البيولوجية. ٧٨ مريض مصاب بسرطان الغدد الليمفاوية تم تصويرهم عن طريق المسح الذري البوزيتروني والأشعة المقطعية قبل بدء العلاج و تم التصوير مرة أخرى بعد ٦ جلسات من العلاج الكيميائي. تم تحليل صور الكبد قبل وبعد العلاج حتى يمكننا معرفة مدى تأثير العلاج الكيميائي عليه. وجد أن ٤٥ مريض تم حدوث تغيير في الكبد. هذه التغييرات كانت تغييرات شكلية ووظيفية. التغييرات الشكلية كانت ملموسة من خلال القياس الكمي لأشعة اكسالتى تم امتصاصها عن طريق الكبد في صورة المقطعية وكذلك كان هناك تغيير في حجم الكبد. و التغييرات الوظيفية كانت ملموسة من خلال قياس كمية المادة المشعة التي امتصها الكبد و كذلك تم قياس تغيير الأيض. كل هذه التغييرات أثبتت أن الكبد انتقل من الحالة الطبيعية للكبد التي كانت مثبتة قبل بدء العلاج إلى كبد دهني بعد أخذ العلاج الكيميائي و كلما زادت جلسات العلاج كان التغيير أسوأ. و بالتالي من خلال هذه الدراسة أثبتنا أن بالرغم من أن العلاج الكيميائي من أحد طرق العلاج التي يتبعها طبيب الأورام في علاج مرضى السرطان وخصوصاً مرضى سرطان الغدد الليمفاوية وله تأثير إيجابي على الورم ولكن هنا أثبتنا أنه له تأثير على الكبد كضوء سليم ليس له علاقة بشكوى المريض وأنه تحول من الكبد السليم إلى كبد دهني مع مرور الوقت يمكن أن يتطور إلى تليف الكبد.