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Research Article

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Computed Tomography Liver Spleen Ratio as Predictive Marker of Liver Injury among Adult Filipina Early Breast Cancer Receiving Neoadjuvant Therapy from 2010-2016: A Six-Year Retrospective Study

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Abstract

There is no way to predict development of liver injury in early breast cancer patients during neoadjuvant treatment. It is our aim to determine such by determining Computed tomography liver spleen ratio (LS ratio) and comparing it to liver function test.

Methods: *Retrospective review for Stage I-III invasive breast cancer. Computed tomography LS ratio was reviewed by one radiologist. LS ratio cut off values were tested of their accuracy wherein computed AUC of > 0.70 is considered valid predictive markers.*

Results: *Thirty-five patients were seen with median age of 54, 57% had stage IIIB cancer. Patients' average LS ratio 1.10±0.30 at the start, thenit slightly increased towards the end of the treatment (1.13±0.32). SGPT (37.43 to 35.09, p=0.479) changed from start to end. Liver spleen ratio significantly correlated with SGPT (r= -0.541, p=0.001). At end of treatment, LS ratio is correlated with SGPT (r = -0.464, p=0.005). It has higher sensitivity at start of treatment 100%, cut off 0.52, while end of treatment cut off was 0.87 has higher sensitivity (100%) in predicting liver injury. Liver Spleen ratio at end of treatment showed higher accuracy (AUC =0.597) indicating the LS ratio can be utilized as marker for predicting liver injury.*

Conclusion: *End of treatment, liver injury was seen in those receiving anthracycline- based regimen. Liver spleen ratio is significantly correlated with SGPT. Liver spleen ratio at end of treatment showed higher accuracy indicating the LS ratio be utilized as marker for predicting liver injury.*

Keywords: Neoadjuvant chemotherapy, Liver spleen ratio, CT scan, Breast cancer, Liver injury

Introduction

Background

One of the limiting factors for the treatment of cancer is its toxicity. Nearly all treatment is metabolized by the liver, hence vigilant monitoring of liver function test can't be over emphasized. Paradigm shift from adjuvant to neoadjuvant chemotherapy is rooted in observations of tumor kinetics and the hypothesis of micro metastatic disease present in the early stages of breast malignancy. Neoadjuvant treatment is given to decrease the tumor burden facilitating breast conservation in selected patients without significant increases in local recurrence. Response to therapy has proven to be a strong predictor of outcome, with patients achieving pathologic complete response (pCR) demonstrating improved survival compared with those achieving less than a pCR. Hence neoadjuvant treatment is given to early non-metastatic breast cancer patients.

With the goal of a complete pathologic response in mind for neoadjuvant therapy, an important factor to consider in the selection of chemotherapy regimen is organ function. Apart from complete blood count and renal function determination, the liver function test is also required to carefully assess the patient to determine which drugs may or may not be appropriate, and which drug doses should be modified. It is important for the oncologist to determine the difference between liver abnormalities due to the therapy itself rather than presence of progressive disease. Chemotherapy and hormonal therapy can bring about different forms of liver injury to patients. Toxic liver injury may result into any known pattern of injury, including necrosis,

steatosis, fibrosis, cholestasis, and vascular injury [1]. However there is no predictor yet of knowing who among these patients receiving cytotoxic drugs can develop liver injury. International organizations recommend screening patients for Hepatitis B Virus infection prior to cancer chemotherapy, especially patients at high risk [2-5]. High risk patients are all individuals born in areas of high or intermediate prevalence and specifically all countries within Asia. Prevalence of Hepatitis B infection in areas of high endemicity such as the Asia-Pacific region approaches to 20%; whereas, in Australia less than 1% of the population are HBsAg positive [6-8].

Significance

Fatty liver disease is an early marker for liver injury. It can be reliably diagnosed using CT scan of abdomen using non enhanced CT scan using the liver spleen (LS) ratio of <1.0. This paper aims todetermine the association of baseline Computed tomography liver spleen ratio to the liver function test pre and post neoadjuvant treatment. It is the goal of the researcher to draw out conclusion from this research who among those early breast cancer to develop liver injury. Since there is no local nor international published data that determine the risk of developing liver injury by using CT spleen ratio, it is main goal to do so. Neoadjuvant therapy is given to virgin cases of breast cancer who have not received treatment before, making these subset of patients a fairly suited for the study. Predicting those patients who from the start is at risk of liver injury can warn the oncologist to have dose modification, rigid follow up of liver function or give liver supplements to take care of the patient.

Research Question

Can computed tomography liver spleen ratio be a predictive marker in the development of liver injury among early breast cancer?

General Objective

To determine whether CT liver spleen ratio hounsfield unit pre-treatment is a clinically valid marker of hepatic injury following neoadjuvant therapy for early breast cancer.

Specific Objectives

i. To describe the patients' profile
ii. To determine the CT liver spleen ratio pre and post neoadjuvant treatment.
iii. To determine theSGPT, SGOT, and total bilirubin values before and after neoadjuvant treatment as indicators of liver injury.
iv. To determine which treatment protocol has the highest risk of developing liver injury.
v. To determine if there is correlation between liver spleen hounsfield unit and liver function test before and after neoadjuvant treatment.
vi. To determine the accuracy of CT liver spleen ratio cut off values such as sensitivity, specificity, positive and negative predictive values as predictor of liver injury.
vii. To construct the Area under Curve plot of CT liver spleen ratio cut off values as predictor liver injury.

Definition of Terms

Hounsfield unit

A linear transformation of the original linear attenuation coefficient measurement into one in which the radiodensity of distilled water at standard pressure and temperatureis defined as zero Hounsfield units (HU), while the radiodensity of air at STP is defined as -1000 HU. It is a quantity commonly used in computed tomogrsaphy scanning to express CT numbers in a standardised and convenient form.

Early breast cancer

Breast cancer is categorized as Stage I, II (A or B), III (A, B, or C), or IV. The stage is based on the size of the tumor and whether the cancer has spread. Stages I, IIA, IIB, and IIIA are considered "early-stage" breast cancer and refer to cancers that may have spread to nearby lymph nodes but not to distant parts of the body.

Neoadjuvant treatment

Treatment before surgery, be it chemotherapy, hormonal or targeted therapy.

Methodology

Study Design

This is a retrospective validity chart review study.

Study Setting

This study was conducted in a 650 bed capacity, tertiary hospital in Quezon City Philippines.

Study Population

All breast cancer patients with CT scan of upper abdomen done before and after neoadjuvant therapy.

Inclusion

i. Women more than 18 years old
ii. Histologic diagnosis of invasive breast cancer
iii. Stage I-III breast cancer who received neoadjuvant therapy

Exclusion

iv. Metastatic breast cancer
v. Known intrinsic liver disease
vi. History of jaundice and hepatitis

Data Collection

Early breast cancer patients who had her Abdominial CT scan done in our institution both before and after her neoadjuvant treatment were all included. Review of records from the Hospital's Web Ambassador, a computer system that archives CT scan studies, was done to patients included in the study. One radiologist was made to review the scans and was made to get the Hounsfield unit for both the liver and spleen. Transaminases were also reviewed before and after neoadjuvant treatment. Neoadjuvant treatment protocol of the included patients were then reviewed.

Data Analysis

Patients' age, LS ratio, and liver injury parameters were described using mean and standard deviations while cancer stage and liver injury were expressed in frequency and percentages. In testing the changes of average values of LS ratio as well as liver injury parameters from pre to post therapy, Paired t-test was used. Moreover, in determining the correlation among LS ratio and all the liver injury parameters, Pearson r product moment correlation. Any associated p-values lesser than 0.05alpha were considered significant. Also, the LS ratio cut off values were tested of their accuracy in terms of sensitivity, specificity, negative, and positive predictive values wherein a computed AUC of > 0.70 is considered significantly valid predictive markers. IBMSPSS ver 21 and NCSSPASS 2000 were used as software.

Study Limitation

Majority of our neoadjuvant patients from 2013-2016 had their CT scan done outside the institution. CT scan not done at our institution was not included in our study hence limiting the number of patients used in this study.

Results

From 2013-2016, there were only 34 early breast cancer patients who had their CT scan of abdomen done at our institution both before and after neoadjuvant therapy. Average age was 53.91 years old, 50% had stage IIIB cancer, while 11.1% had stage IIIA. Stage IIA and IIB each were 8.3% (Table 1).

Table 1: Patient Profile

Patients' Characteristics	Descriptive n=35
Age, years mean±sd	53.91±11.66
Cancer Stage	
IIA	3[8.3%]
IIB	3[8.3%]
III	1[2.8%]
IIIA	4[11.1%]
IIIB	18[50%]
IIIC	1[2.8%]
no data	6[16.7%]

Table two describes the patient's liver spleen, SGPT, DGOT and total bilirubin levels before and after neoadjuvant therapy. Patients' average liver spleen ratio was 1.10±0.30 at the start, then, it slightly increased towards the end of the treatment (1.13±0.32). SGPT (37.43 to 35.09, p=0.479) changed from start to end of treatment. Computed p-value lesser than 0.05alpha, the change from pre to post is noted to be significant.

Table 2: Patients' LS Ratio, SGPT, SGOT, and Total Bilirubin at Pre to Post NeoadjuvantTherapy

Start of treatment			End of treatment		
Assessment	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**p-value**
Liver / Spleen					
Liver HU	48.00	11.36	49.74	14.08	0.391
Spleen HU	44.61	6.71	44.26	5.07	0.773
L/S Ratio	1.10	0.30	1.13	0.32	0.573
Liver					
SGPT	37.43	19.31	35.09	14.93	0.479
SGOT	25.51	8.92	27.51	10.53	0.311
Total Bilirubin	0.40	0.17	0.40	0.17	0.976

Table 3 describes the drug induced liver injury rate for each treatment protocol used in the neoadjuvant therapy. Higher rates of drug induced liver injury at the start of treatment were as follows, 1(100%) with Docetaxel-Trastuzumab, FAC regimen 1(100%), and TAC regimen (11.1%). End of treatment, drug induced liver injury were noted among those with AC (50%), FAC (100%), Epirubicin, Docetaxel (25%), and TAC (11.1%).

Table 3: Liver Injury Rate per Treatment Protocol

TREATMENT RECEIVED	Total	Start of Treatment		End of Treatment	
	No. of Cases	Liver Injury	No Liver Injury	Liver Injury	No Liver Injury
AC	2	0[0%]	2[100%]	1[50%]	1[50%]
AC- Docetaxel	8	0[0%]	8[100%]	0[0%]	8[100%]
Docetaxel-Trastuzumab	1	1[100%]	0[0%]	0[0%]	1[100%]
Docetaxel, FEC	1	0[0%]	1[100%]	0[0%]	1[100%]
Docetaxel, FEC + Trastuzumab	5	0[0%]	5[100%]	0[0%]	5[100%]
Epirubicin, Docetaxel	4	0[0%]	4[100%]	1[25%]	3[75%]
FAC	1	1[100%]	0[0%]	1[100%]	0[0%]
FEC	1	0[0%]	1[100%]	0[0%]	1[100%]
Goserelin, Letrozole	1	0[0%]	1[100%]	0[0%]	1[100%]
Letrozole	1	0[0%]	1[100%]	0[0%]	1[100%]
Paclitaxel-Carboplatin	1	0[0%]	1[100%]	0[0%]	1[100%]
TAC	9	1[11.1%]	8[88.9%]	1[11.1%]	8[88.9%]
Total	35	3[8.6%]	32[91.4%]	4[11.4%]	31[88.6%]

AC- Doxorubicin + Cyclophosphamide; FEC- 5 Fluorouracil, eprubin, Cyclophosphanide; TAC- Doxorubicin, Docetaxel, Cylophosphamide

Liver spleen (LS) ratio is significantly correlated with SGPT (r= -0.541, p=0.001). At end of treatment, LS ratio is correlated with SGPT (r = -0.464, p=0.005) . LS ratio has higher sensitivity at start of treatment 100% at cut off 0.52, while at end of treatment the cut off was 0.87 has higher sensitivity (100%) in predicting liver injury (Table 4). Table five showed the accuracy of liver spleen ratio as predictors of liver injury at pre and post neoadjuvant therapy. LS ratio has higher sensitivity at start of treatment 100% at cut off 0.52, while at end of treatment the cut off was 0.87 has higher sensitivity (100%) in predicting liver injury.

Table 4: Correlation of Patients' LS Ratio and Parameters of Liver Injury

L/S Ratio	Correlation	SGPT	SGOT	TOTAL BILIRUBIN	SGPT	SGOT	TOTAL BILIRUBIN
L/S Ratio (before neoadjuvant therapy)	Pearson Correlation	-.541**	-0.107	-0.253	-0.253	-.431**	-0.137
	p-value	0.001	0.541	0.142	0.142	0.01	0.434
L/S Ratio (after neoadjuvant therapy)	Pearson Correlation	-0.33	-0.005	-0.059	-.464**	-0.199	-0.075
	p-value	0.053	0.976	0.735	0.005	0.251	0.668

Table 5: Accuracy of LS Ratio as Predictors of Liver Injury at Pre to Post Neoadjuvant Therapy

LS Ratio Cut off Values				
Tested as Predictors of Liver Injury	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**
Start of Treatment				
0.52	100.0%	3.1%	8.8%	100.0%
1.14	33.3%	56.3%	6.7%	90.0%
1.76	0.0%	100.0%	0.0%	91.4%
End of Treatment				
0.13	100.0%	3.2%	11.8%	100.0%
0.87	100.0%	19.4%	13.8%	100.0%
1.61	0.0%	100.0%	0.0%	88.6%

Based on area under the curve (Figure 1), LS ratio at the end of treatment showed higher accuracy (AUC =0.597) as compared to the AUC at the start of the treatment (AUC=0.46). Indicating that the LS ratio can be utilized as a marker for predicting liver injury.

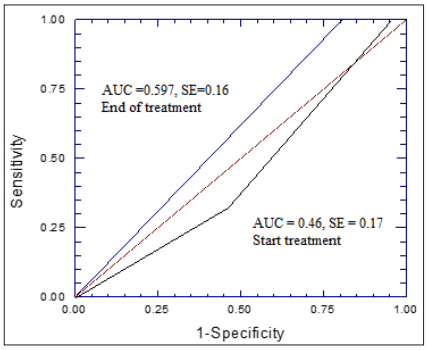

Figure 1: AUC ROC of LS Ratio as Predictor of Liver Injury at Pre to Post Neoadjuvant

Discussion

Liver injury secondary to chemotherapeutic drugs are mostly idiosyncratic. It is due to immunologic mechanisms or variations in host metabolic response [9]. These reactions are not typically dose-dependent. Less common are dose-dependent, predictable toxic effects of a medication or its metabolites.

Chemotherapeutic agents used for breast cancer have different mechanism of action for bringing about liver injury. Cyclophosphamide is an uncommon hepatic toxin, and only a few reports of elevated hepatic enzymes are attributed to the drug [10-15]. This effect is likely due to an idiosyncratic reaction rather than direct toxicity. 5-Fluorouracil does not seem to cause liver damage when given orally than given intravenously [16]. Doxorubicin, is extensively metabolized in the liver. It acts through DNA intercalation and free radical formation. It is extensively metabolized in the liver, and liver antioxidant capacity, including that provided by glutathione production [17]. After administration, increases in AST, ALT, and bilirubin were seen, with focal infiltration by inflammatory cells and steatosis on liver biopsies. Paclitaxel and docetaxel work by binding to microtubules rather than tubulin dimers. Both are extensively excreted by the liver, and caution is warranted in patients with liver impairment. With paclitaxel, elevation from baseline hepatic functions (bilirubin, 8%; alkaline phosphatase, 23%; transaminase, 33%) was seen in 4% to 17% of patients treated with doses of less than 190 mg/m2 and in 16% to 37% of patients treated at higher doses [18]. Carboplatin is a cisplatin derivative developed to meet the need for a platinum compound with a better therapeutic index. A case of carboplatin-induced liver failure has been reported [19]. Although multiple other medications were given as well, the potential role of carboplatin in the production of liver disease deserves mention.

Administration of chemotherapy entails the vigilant monitoring of hematologic, renal and hepatologic function. Liver injuries brought about by these chemotherapeutic agents can be monitored by getting the liver function test however gold standard diagnosis is still liver biopsy. Additional biopsy could be grueling for a cancer patient. Hence the investigator is looking for adjunct ways of for predicting if not diagnosing liver injury. To date, there is no way yet of predicting whom among the cancer patients undergoing chemotherapy would develop liver injury. There are other parameters of determining liver injury such as the liver spleen ratio using the houndsfield unit in the CT scan. This however was based on presence of liver fat [20].

Neoadjuvant early breast cancer patients are the subject of this investigation since they have not received any chemotherapeutic agents yet and have no metastasis which is important baseline parameters for us to determine the idiosyncratic effects of these chemotherapeutic agents to the liver. Determination of the hounsfield

unit to get the liver spleen ratio via the archived CT scan of the included patients was done for this study and is indeed reproducible. Backtracking the liver function tests that were also archived in the hospital's computer system were then analyzed to determine its significance and its correlation to the liver injury noted in the LS ratio. It was 2013 when our institution fully embraced neoadjuvant treatment for early breast cancer patients hence the study setting was started at this point. Although we only had 35 patients included in the study, these patients had both pre and post neoadjuvant CT scans done at our institution which was readily retrieved and tested for the LS ratio by the same one radiologist.

This study showed majority of our patients were stage IIIB and stage IIIA patients. For very early breast such as Stage I or Stage II patients, NCCN guidelines recommend that routine imaging is not indicated if there is no sign or symptom of metastatic disease [21]. Liver ultrasound along with chest x-ray are recommended for newly diagnosed breast cancer work up evaluation for metastatic disease [22]. CT scan of abdomen was only recommended if patient has elevated alkaline phosphatase and liver function test.

This study also showed higher rate of changes in baseline SGPT levels when patients received anthracycline and/or taxane. Liver spleen ratio determination showed an increase from baseline (before neoadjuvant) chemotherapy when compared to the LS ratio after neoadjuvant therapy. It is demonstrated in Table four that changes in LS ratio was correlated with the changes in SGPT after neoadjuvant therapy. LS ratio at the end of neoadjuvant therapy was shown to have higher accuracy as depicted in table five.

Conclusion

Higher rates of liver injury at the start of treatment were seen those given anthracycline and taxane based chemotherapy. Liver spleen ratio is significantly correlated with SGPT. LS ratio at the end of treatment showed higher accuracy indicating the LS ratio be utilized as marker for predicting liver injury.

Recommendation

The researcher strongly recommends the inclusion of determination of liver spleen ratio in the CT scan reports of patients undergoing chemotherapy. As shown in this study, it may be used as marker for predicting liver injury as it has positive correlation with the increase in SGPT levels post treatment.

Future research endeavors on the local data on advance or metastatic breast cancer patients and its association with changes in LS ratio after treatment. To improve generalizability, adequate sample size and study period is also encouraged.

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