

## Evaluation of Breast Cancer Radiotherapy Induced Liver Fibrosis by Elastography

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### ABSTRACT

**AIM:** Radiotherapy is an essential part of breast cancer standard therapeutic regimen. Based on anatomical vicinity, liver is susceptible to radiation induced injury at doses more than 30 gray. This study designed to determine the relation between breast cancer radiotherapy and liver fibrosis.

**METHODS:** In this case control descriptive study, the intervention group selected among patients whom underwent radiotherapy for breast cancer. The patients evaluated for viewpoint of BMI, age and liver enzymes and the ones with any kind of chronic liver disease excluded. Overall 60 breast cancer cases divided into 3 groups as:

breast cancer without radiotherapy (group A) and left or right breast cancer treated with radiotherapy (groups B and C respectively). All of the patients evaluated by liver fiber scan.

**RESULTS:** Average age of patients in groups A, B and C were 47±8, 49±10 and 49±10 years respectively ( $P=0.560$ ). Mean BMI as kg/m<sup>2</sup> were similar among 3 groups (A 26±2, B 28±3 and C 24±4) ( $P=0.021$ ). Average sessions of radiotherapy were 20±9 and 27±6 in groups B and C respectively with no course at all in group A. Average score of fiber scan as KPa in groups A, B & C were 6±2.3, 7.2±2.6 and 6.9±2.9 respectively ( $P=0.38$ ).

**CONCLUSION:** In this study we found no meaningful relation between breast cancer radiotherapy and liver fibrosis in spite of anatomical vicinity of breast and liver. It seems that breast radiotherapy even at doses higher than 40 Grays has no effect on liver stiffness although it has been advised to be careful and in case of any disturbance in liver function tests, supporting and diagnostic measures be performed.

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**Key words:** Breast cancer; Radiotherapy; Liver fiber scan

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### INTRODUCTION

Breast cancer is the most common cancer among women and responsible of 12.6 % of all cases of cancer in them. Breast cancer mortality has steadily declined since 1990 due to improvements in diagnosis and treatment. 5-year survival rate for breast cancer is now up to 98% for the focal stage and up to 81% for the regional stage<sup>[1,2,3]</sup>. Radiation therapy is a mandatory and elemental part of

standard therapeutic regimen for breast conservation and an essential part of management of the microscopic cancer remnants<sup>[4,5,6]</sup>. For each breast cancer patient average sort of 50 Gy radiotherapy requires which divided to 1.8-2 Gy in each session<sup>[7]</sup>.

Indications of breast cancer radiotherapy include: Ductal carcinoma insitu, lumpectomy and modified radical mastectomy with positive margins or lymph nodes involvement. In patients with positive estrogen receptor, Tamoxifen is also used. The most common side effects of tamoxifen include hot flashes, hypertension, edema, nausea, increase in bilirubin, AST, and rarely fatty liver (less than 1%)<sup>[8]</sup>. Radiation induced hepatitis is usually induced 4-8 weeks after irradiation with a doses more than 30 Gy (3,000 Rad) in 6-66% of cases. Radiation can cause a non-specific occlusive venular disease in the liver, leading to liver fibrosis by releasing of TGF-B1<sup>[9-13]</sup>.

Radiotherapy (RT) of the liver tumors has a limited role because of poor liver tolerance to radiation. Radiation dose of 30-33 Gy has 5% risk of radiation -induced liver injury (RILD) and this risk raises to approximately 50% as the dose reaches 40 Gy<sup>[14]</sup>. After recurrent courses of radiotherapy, Liver damage diagnoses as radiation induced hepatitis, which is better to addressed as radiation induced liver damage (RILD) because usually there is no histologic evidence of hepatitis<sup>[15]</sup>. Causes of NAFLD can be divided into two basic groups: one as fatty liver related causes and the other as secondary causes (toxins and drugs such as Tamoxifen)<sup>[16,17,18]</sup>.

Liver biopsy is the gold standard for assessing liver fibrosis<sup>[19]</sup>, but the role of liver biopsy in confirmation of diagnosis of NAFLD is controversial<sup>[20,21]</sup>. NAFLD is usually diagnosed after ruling out other causes of chronic liver disease by clinical examination and using laboratory data<sup>[22]</sup> and given the high prevalence of NAFLD, a liver biopsy is impractical in this case<sup>[21]</sup>.

The purpose of this study is to evaluate the prevalence of steatohepatitis and liver fibrosis in patients with breast cancer undergoing breast radiotherapy, and to find difference for viewpoint of tumor location in right or left breast if any.

## METHODS

In this case control descriptive study, all of the breast cancer patients whom referred to oncology department of Ahwaz Golestan hospital in a 4 months period selected. Patients were examined in terms of weight, Height, blood pressure, any complicating liver disease and viral or autoimmune hepatitis, metabolic situation including Diabetes Mellitus and hyperlipidemia and also history of alcohol and or hepatotoxic drugs consumption. After preliminary evaluation and obtaining a signed consent form and 2 weeks after termination of course of radiotherapy, all of the patients sent to Elastography center to determine the extent of liver fibrosis by performing liver fiber scan.

To determinate significant fibrosis and liver cirrhosis on elastography we used cut off level of 8.7 to 10.3 KPa as F3-F4 and 11.5 KPa respectively<sup>[23]</sup>. EchoSens FibroScan device model 502 (made in France) was used for Elastography liver. Inability to performing liver Elastography due to abundant adipose tissue in the thoracic area because of lack of probe XL was the limitations of this study. Finally the results of liver elastography among 3 groups compared together and the statistical analysis of matching the age and BMI, receiving or not Tamoxifen and radiotherapy sessions in each group were reviewed again.

Patients who consumed alcohol more than 20 g/d, had ALT level more than 120 before course of radiotherapy, advanced liver disease, previous history of gastrointestinal surgery, Total parental nutrition during the past six months, autoimmune or viral hepatitis,

Wilson, Hemochromatosis, hepatotoxic drugs usage during last 6 months, heart failure, Hepatic vascular disorders such as Budd-Chiari syndrome or had any liver mass were excluded.

According to lack of any similar study about the prevalence of liver fibrosis in patients undergoing radiation therapy for breast cancer, we performed this study as a pilot and finally 60 patients divided in three groups (patients undergoing right and left breast cancer radiotherapy and breast cancer without radiotherapy) were matched for demographic characteristics and enrolled the study. The data were analyzed by using SPSS software version 19. Mean of Quantitative descriptive variables and standard deviation were calculated.

In univariate analysis, the Chi-square and Fisher exact test used for qualitative variables and Pearson correlation test was also used for correlation between quantitative variables. An informed consent form was signed by all of patients before participating in study and during the course, they were free to leave study if they wish.

## RESULTS

From 60 breast cancer patients who have been examined in this study, 20 patients had not received radiotherapy (group A), 20 patients had left breast radiotherapy (group B) and the rest of patients had right breast radiotherapy (group C).

The mean age of the patients was 47±8 (95% CI, 44-51), 49±10 (95% CI, 44-53) and 49±10 (95% CI, 44-53) years, in Groups A, B and C respectively, whit no statistically significant difference (*P* value=0.560) (Table 1). Mean BMI was 26±2 (95% CI, 24-27), 28±3 (95% CI, 26-29) and 24±4 (95% CI, 22-26) among 3 groups (A, B, C) respectively (*P* value=0.021). The mean waist circumference of patients were 82±9 (95% CI, 77-87), 86±10 (95% CI, 81-91) and 79±13cm (95% CI, 73-85) respectively, in groups A, B and C, which was not statistically significant different (*P* value=0.211).

Average AST/ALT ratio were 1.13±0.3 (95% CI, 0.98-1.27), 1.09±0.29 (95% CI, 0.95-1.23) and 1.14±0.31 (95% CI, 1-129) respectively (*P* value=0.862). Mean FBS of patients were 99±25 (95% CI, 87-111), 107±37 (95% CI, 89-124) and 102±19mg/dL (95% CI, 92-111) respectively in Groups A, B and C (*P* value=0.691).

The mean duration of Tamoxifen usage was 1.2±1.4 (95% CI, 0.5-1.9), 2.1±1.4 (95% CI, 1.4-2.7) and 2.3±2.1 years (95% CI, 1.3-3.3) among 3 groups respectively (*P* value=0.114). Average number of radiotherapy sessions in groups B and C were 20±9 (95% CI, 16-25) and 27±6 (95% CI, 24-29), respectively, with no radiotherapy at all in group A (*P* value=0.000). Mean liver elastography of patients were 6±2.3 (95% CI, 4.9-7.1), 7.2±2.6 (95% CI, 5.9-8.4) and 6.9±2.9 KPa (95% CI, 5.5-8.3) in groups A, B and C respectively (*P* value=0.340).

According to table 2, in breast cancer patients with no radiotherapy (group A), 17 patients (85%) classified as F0-2 and 3 (15%) as F3-4. These results in Left breast cancer patients (group B) were 14 patients (70%) as F0-2 and 6 (30%) as F3-4. In right breast cancer patients (Group C), 16 (80%) as F0-2 and 3 (20%) as F3-4 (*P*-value=0.5) and the correlation between liver stiffness and the degree of radiation effect was observed in transient Elastography.

In patients treated with Tamoxifen, 47 patients (78.3 %) patients had Elastography results F0-2 (Table 3) with a mean duration of Tamoxifen usage was 1.9±1.8 years. 13 patients (21.7 %) had Elastography F3-4 with a mean duration of Tamoxifen usage as 1.6±1.3 years. In breast cancer patients receiving chemotherapy, 47 patients (78.3 %) had Elastography F0-2. The mean number of chemotherapy sessions was 4±3 sessions per patient and, 13 patients (21.7%) reported as Elastography F3-4, respectively. The mean number of chemotherapy sessions was 3±3.

**Table 1** Comparison of clinical data between patients with breast cancer who had not received radiotherapy (group A), patients with left breast cancer radiotherapy (group B) and right breast cancer radiotherapy (group C).

Data	Group A		Group B		Group C		Total		p value
	MEAN±SD	95%CI	MEAN±SD	95%CI	MEAN±SD	95%CI	MEAN±SD	95%CI	
AGE(y)	47±7.5	44-51	49±10.3	44-53	46±8.2	42-49	47±8.7	45-49	0.560
BMI	26.2±2.9	24-27	28.1±3.9	26-29	24.7±4.2	22-26	26.3±3.9	25-27	0.021
ABD.CIRC (cm)	82±10	77-78	86±10	81-91	79±13	73-85	82±11	79-85	0.211
Tamoxifen (y)	1.25±1.4	0.5-1.9	2.1±1.4	1.4-2.7	2.35±2.1	1.3-3.3	1.9±1.7	1.4-2.3	0.114
RT.COURSE (COURSE)	0±0	0	20±9	16-25	27±6	24-29	15±13	12-19	0.000
Chemotherapy (COURSE)	3.2±2.6	1.9-4.4	4.8±2.8	3.4-6.1	4.9±3.7	3.1-6.6	4.3±3.1	3.4-5.1	0.162
AAR	1.1±0.3	0.9-1.2	1±0.29	0.9-1.2	1.1±0.3	1-1.2	1.1±0.3	1-1.2	0.862
FBS	99±25	87-111	107±37	89-124	102±20	92-111	102±28	95-110	0.691
TG	166±30	151-180	146±40	127-165	153±60	125-182	155±45	143-167	0.389
APRI									
BARD	1.2±0.6	0.9-1.5	1.7±0.6	1.3-2	1.3±0.8	0.9-1.6	1.4±0.7	1.2-1.6	0.094
BAAT	1.6±0.8	1.2-2	1.9±1.2	1.3-2.4	1.1±0.9	0.6-1.5	1.5±1.0	1.2-1.8	0.045
FIBROSCAN (Kps)	6±2.3	4.9-7.1	7.2±2.6	5.9-8.4	6.9±2.9	5.5-8.3	6.7±2.6	6-7.4	0.340

APRI (AST to PLT Ratio Index): (AST/ULN)/PLT ×100; AAR: AST/ALT Ratio; BARD: BMI≥28; AAR≥0.8, DM2. BAAT: BMI≥28, AGE≥50, ALT >×2ULN, TG≥155.

The relationship between Tamoxifen usage duration, number of radiotherapy sessions and chemotherapy courses with the degree of liver stiffness as observed in transient Elastography was not meaningful (*P* Value=0.59, 0.38, 0.31 respectively).

From 32 patients who had been taking tamoxifen for less than or equal to one year, 26 patients (81.2%) had Elastography results of F0-2, and 6 patients (18.8%) reported as F3-4 (Table 4). Among 28 patients who had been taking tamoxifen for more than one year, 21 patients (75%) had Elastography F0-2 and 7 (25 %) had Elastography F3-4.

In total there was not any significant relation between duration of Tamoxifen usage and degree of liver stiffness based on transient Elastography (*P*=0.558). Overall association between BMI and the degree of liver stiffness in transient Elastography was statistically significant (*P* value=0.023) (Table 5).

**Table 2** Comparison of liver stiffness in Transient Elastography between patients with breast cancer had not received radiotherapy (group A), patients with left breast cancer radiotherapy (group B) and of the right breast cancer radiotherapy (group C).

Elastography	Group A		Group B		Group C		Total	
	n	%	n	%	n	%	n	%
F0-F2	17	85	14	70	16	80	47	78.3
F3-F4	3	15	6	30	4	20	13	21.7
Total	20	100	20	100	20	100	60	100
P value	0.503							

**Table 3** Comparison of liver stiffness in Transient Elastography with Treatment Time.

Elastography	F0-F2		F3-F4		P value
	MEAN±SD	95%CI	MEAN±SD	95%CI	
Tamoxifen(y)	1.96±1.83	-0.8-1.3	1.69±1.37	-0.7-1.2	0.315
RT.COURSE (COURSE)	15.9±13.5	-8.5-8.2	16.0±12.5	-8.4-8.2	0.387
Chemotherapy (COURSE)	4.4±3.1	-1.4-2.5	3.8±3.2	-1.5-2.7	0.591

**Table 4** Comparison of liver stiffness in Transient Elastography with Tamoxifen Treatment Time.

Elastography	F0-F2		F3-F4		Total	
	n	%	n	%	n	%
Tamoxifen Treatment Time						
one year ≥	26	81.3	6	18.8	32	53.3
One year <	21	75	7	25	28	46.7
Total	47	78.3	13	21.7	60	100
P-value	0.558					

**Table 5** Comparison of liver stiffness in Transient Elastography with BMI (kg/m<sup>2</sup>).

BMI	Elastography		F3-F4		Total	
	n	%	n	%	n	%
28>	31	88.6	4	11.4	35	58.3
28≤	16	64	9	36	25	41.7
Total	47	78.3	13	21.7	60	100
P value	0.023					

## DISCUSSION

Cancer is one of the most important and healthcare issues among the whole world<sup>[1]</sup>. Breast cancer is the most common cancer among women<sup>[3]</sup>. The standard radiation therapy is an essential component of breast conservative therapy to eradicate microscopic residual cancer cells<sup>[4,5,6]</sup>. Due to proximity to the liver Breast radiotherapy potentially can cause hepatitis or liver damage caused by radiation<sup>[8-12]</sup>.

Our findings indicate that among breast radiation and elasticity (stiffness) of the liver, there is no significant correlation (*P* value=0.5) and the relationship between the breast radiotherapy sessions and liver elasticity was not significant. Contrary to the findings of the study, in 1991, by Emami B *et al* radiation therapy of liver tumors at a dose of 30-33 Gy, carries a 5 % risk and radiation dose of 40 Gy, 50 % risk for liver damage induced by radiation (RILD)<sup>[14]</sup>.

Based on Lawrence TS *et al* study (1995), liver damage could present after repeated courses radiation as RILD and the radiation protection measures are important to prevent hepatitis<sup>[15]</sup>. In 1997 Robertson *et al* found no significant relation between liver radiotherapy and RILD<sup>[24]</sup>. As the previous studies evaluated the direct effect of radiotherapy on liver tissue and with respect of anatomical vicinity of breast to liver, the potential hazard of breast radiotherapy on liver should be minor if any at all and reversible. In this study, no significant association was found between Tamoxifen usage and liver stiffness (*P* value = 0.31) which could be predictable when considering the risk of Tamoxifen induced fatty liver of less than one percent<sup>[8]</sup>.

## CONCLUSION

In this study, no significant relationship was observed between liver stiffness and the degree of radiation therapy for breast cancer despite the proximity of the liver even with doses higher than 40 Gy. Although we recommend to be cautious in case of any symptom or abnormal liver function tests.

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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